EXHIBIT A

Fixed-Dose Trial of the Single Isomer SSRI Escitalopram in Depressed Outpatients

William J. Burke, M.D.; Ivan Gergel, M.D.; and Anjana Bose, Ph.D.

Background: Escitalopram is the single isomer responsible for the serotonin reuptake inhibition produced by the racemic antidepressant citalopram. The present randomized, double-blind, placebo-controlled, fixed-dose multicenter trial was designed to evaluate the efficacy and tolerability of escitalopram in the treatment of major depressive disorder.

Method: Outpatients with an ongoing DSM-IV major depressive episode (N = 491) were randomly assigned to placebo, escitalopram, 10 mg/day, escitalopram, 20 mg/day, or citalopram, 40 mg/day, and entered an 8-week double-blind treatment period following a 1-week single-blind placebo lead-in. Clinical response was evaluated by the Montgomery-Asberg Depression Rating Scale (MADRS), the 24-item Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI) scales, the Hamilton Rating Scale for Anxiety (HAM-A), and patient-rated quality-of-life scales.

Results: Escitalopram, at both doses, produced significant improvement at study endpoint relative to placebo on all measures of depression; significant separation of escitalopram from placebo was observed within 1 week of double-blind treatment. Citalopram treatment also significantly improved depressive symptomatology compared with placebo; however, escitalopram, 10 mg/day, was at least as effective as citalopram, 40 mg/day, at endpoint. Anxiety symptoms and quality of life were also significantly improved by escitalopram compared with placebo. The incidence of discontinuations due to adverse events for the escitalopram 10 mg/day group was not different from the placebo group (4.2% vs. 2.5%; p = .50), and not different for the escitalopram 20 mg/day group and the citalopram 40 mg/day group (10.4% vs. 8.8%; p = .83).

Conclusion: Escitalopram, a single isomer SSRI, is well-tolerated and has demonstrated antidepressant efficacy at a dose of 10 mg/day.

(J Clin Psychiatry 2002;63:331–336)

Received Mar. 26, 2001; accepted Jan.3, 2002. From the Department of Psychiatry, University of Nebraska Medical Center, Omaha (Dr. Burke) and Forest Laboratories, New York, N.Y. (Drs. Gergel and Bose).

This study was supported by a grant from Forest Pharmaceuticals, Inc. Statistical support was provided by James Jin, Ph.D.

Corresponding author and reprints: William J. Burke, M.D., 985580 Nebraska Medical Center, Omaha, NE 68198–5580.

The selective serotonin reuptake inhibitor (SSRI) antidepressants are recommended as first-line antidepressants, due mainly to their superior safety profile relative to their therapeutic predecessors, the tricyclic antidepressants.[1] Despite the well-known heterogeneity of the currently available SSRIs, and even some comparative trial data indicating differences in efficacy within the class,[2] no single SSRI is recognized as an obvious first-line choice. It has been suggested that some subsets of patients respond better to one SSRI than to another.[3–5]

Chirality potentially offers one method to improve upon the SSRI class: if all the serotonin reuptake inhibitory activity of a racemic SSRI antidepressant resides in one isomer, that single isomer would be expected to be more potent than the racemate, and it might also be more selective.[6,7] Thus, the clinical development of that single isomer could improve both risks and benefits over the original antidepressant compound.

Escitalopram is the *S*-enantiomer of the SSRI citalopram, a racemic compound that has been demonstrated to be effective in the treatment of depression, panic disorder, premenstrual dysphoric disorder, and obsessive-compulsive disorder.[8–10] Substantial evidence indicates that escitalopram is responsible for the therapeutic efficacy of the racemate. For example, in vitro pharmacologic studies have demonstrated that escitalopram is more selective than the available SSRIs.[11] Escitalopram is over 100 times more potent as a serotonin reuptake inhibitor than its stereoisomer, *R*-citalopram.[12,13] In vivo studies of antidepressant action also support this conclusion; escitalopram is as efficacious as citalopram in various animal models of depression.[12,14–16] In animal behavioral experiments, escitalopram exhibits at least twice the potency of citalopram.[14] There is also abundant clinical experience with escitalopram as a component of citalopram, which has been used in over 30 million patients with an excellent safety profile (data on file; Forest Laboratories, Inc., New York, N.Y.).

Escitalopram is therefore expected to offer several advantages over citalopram. Escitalopram theoretically should have at least twice the antidepressant potency of citalopram, since the therapeutic effects of citalopram are thought to be dependent upon serotonin reuptake inhibition and escitalopram appears to be responsible for virtually all of the serotonin reuptake inhibition produced by citalopram. Moreover, if any adverse effects of racemic citalopram are attributable to the *R*-enantiomer, they would be avoided in patients treated with the pure *S*-enantiomer. The investigation of the antidepressant effects of escitalopram has thus been pursued with the objective of developing a novel SSRI that might be more potent and/or better tolerated than currently available antidepressant medications. The current multicenter, placebo-controlled study, using citalopram as an active treatment control, examined the safety and efficacy of escitalopram at fixed doses of 10 and 20 mg/day in outpatients with major depressive disorder.

METHOD

A total of 35 centers in the United States participated in this randomized, double-blind, placebo-controlled, multicenter, parallel, fixed-dose study.

Patients

Eligible participants were male or female outpatients, 18 to 65 years of age, with DSM-IV[17] diagnosis of major depressive disorder. Patients were required to meet DSM-IV criteria for a major depressive episode, at least 4 weeks in duration, and to have a minimum score of 22 on the Montgomery-Asberg Depression Rating Scale (MADRS),[18] and a minimum score of 2 on item 1 (depressed mood) of the Hamilton Rating Scale for Depression (HAM-D).[19]

Patients were excluded if they had any DSM-IV Axis I disorder other than major depression, any personality disorder, a history of substance abuse, a suicide attempt within the past year, or evidence of active suicidal ideation (as indicated by a score of at least 5 on item 10 of the MADRS). Women of childbearing potential were included only if they agreed to use a medically acceptable method of contraception; pregnant or lactating women were excluded. No concomitant psychotropic medication was permitted, except zolpidem for insomnia (no more than 3 times per week). The study protocol was approved by the institutional review boards for all participating study centers, and all subjects provided written informed consent.

Study Design

Patients meeting eligibility criteria at a screening visit entered a 1-week, single-blind, placebo lead-in period (1 placebo capsule daily), returning for a baseline visit at the end of the lead-in period. Patients completing the placebo lead-in, who continued to meet all entry criteria, were then randomly assigned to receive 8 weeks of double-blind treatment (1 capsule per day) with placebo, escitalopram, 10 mg/day, escitalopram, 20 mg/day, or citalopram, 40 mg/day.

Throughout the 8-week double-blind treatment period, patients assigned to placebo or to escitalopram, 10 mg/day, received no adjustment of dosage. Patients in the escitalopram 20 mg/day group and in the citalopram group were titrated to their final dose after 1 week of treatment at half of their assigned dose. In order to maintain the blind, all double-blind study medication was administered as 1 capsule per day, regardless of dose or treatment group. No further adjustment of dosage was permitted.

Study visits were conducted after 1, 2, 4, 6, and 8 weeks of double-blind treatment, during which efficacy and safety evaluations were conducted. Efficacy assessments at each visit included the MADRS, the 24-item HAM-D, and the Clinical Global Impressions[20] Improvement and Severity scales (CGI-I and CGI-S). Anxiety symptoms were measured at baseline and at week 8 with the Hamilton Rating Scale for Anxiety (HAM-A).[21] Additionally, patient functioning was assessed at baseline and at week 8 with 2 patient-rated questionnaires: the Center for Epidemiological Studies-Depression Scale (CES-D)[22] and the Quality of Life Questionnaire (QOL), a 16-item instrument derived from the Quality of Life Enjoyment and Satisfaction Questionnaire.[23] For the QOL, higher positive numbers represent better quality of life. Safety measures obtained at every visit included vital signs (after 5 minutes of sitting), body weight, and adverse event monitoring. Electroencephalogram (ECG), physical examination, and laboratory tests were performed at screening and at the end of week 8. All end-of-study assessments were also performed for any patient who discontinued the study prematurely.

Statistical Analysis

The primary statistical approach was a comparison between treatment groups of the change from baseline using the last-observation-carried-forward (LOCF) approach that included all patients who received at least 1 dose of double-blind study medication and had at least 1 postbaseline MADRS assessment. An analysis of patients completing 8 weeks of treatment was also conducted. All presented data are LOCF analyses except where otherwise indicated.

An analysis of covariance (ANCOVA), including treatment, study center, and the treatment by center interaction as factors and the baseline score as covariate, was used for the comparison of the change from baseline to endpoint in all efficacy parameters. The interaction term was dropped from the model if it was not significant at the 10% level. Pairwise comparisons were carried out only if the overall p value (F test) was significant. For the CGI-I, an analysis of variance model (ANOVA) was used. Additional by-visit analyses were carried out for all efficacy parameters using an additive ANCOVA model (ANOVA for CGI-I). Incidence of treatment-emergent adverse events and rate of dis-

Table 1. Baseline Characteristics of Patients With DSM-IV Major Depressive Disorder[a]

Characteristic	Placebo (N = 119)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 118)	Escitalopram 20 mg/d (N = 123)
Age, mean ± SD, y	40.1 ± 10.6	40.0 ± 11.5	40.7 ± 12.3	39.6 ± 12.0
Gender, % female	60	62	70	68
MADRS, mean ± SD	29.5 ± 5.0	29.2 ± 4.5	28.0 ± 4.9	28.9 ± 4.6
HAM-D, mean ± SD	25.8 ± 5.9	25.9 ± 5.9	24.3 ± 6.2	25.8 ± 5.7
CGI-S, mean ± SD	4.2 ± 0.5	4.3 ± 0.6	4.2 ± 0.5	4.3 ± 0.6
Disease course, % recurrent	69	70	69	73

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Change From Baseline (mean ± SEM) Endpoint Values for Efficacy Variables[a]

Outcome Measure	Placebo (N = 119)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 118)	Escitalopram 20 mg/d (N = 123)
MADRS	−9.4 ± 0.9	−12.0 ± 0.9*	−12.8 ± 0.8**	−13.9 ± 0.8**
HAM-D	−7.6 ± 0.8	−9.9 ± 0.9*	−10.2 ± 0.7*	−11.7 ± 0.8**
CGI-I[b]	3.0 ± 0.1	2.6 ± 0.1*	2.5 ± 0.1**	2.4 ± 0.1**
CGI-S	−0.8 ± 0.1	−1.2 ± 0.1*	−1.3 ± 0.1**	−1.4 ± 0.1**
HAM-D, depressed mood item	−0.9 ± 0.1	−1.4 ± 0.1**	−1.3 ± 0.1**	−1.4 ± 0.1*

[a]Abbreviations: CGI-I and CGI-S = Clinical Global Impressions-Improvement and -Severity scales, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]For CGI-I, values represent mean scores after 8 weeks of treatment.
*Significantly different from placebo, $p \leq .05$.
**Significantly different from placebo, $p < .01$.

continuation due to adverse events were analyzed using Fisher exact test. All statistical tests were 2-sided and used a 5% significance level.

The primary outcome measure was the change from baseline in the MADRS total score at week 8. Secondary outcome measures included the change from baseline in the MADRS total score at weeks 1, 2, 4, and 6; the change from baseline in the HAM-D and CGI-S at all visits; and the CGI-I score at weeks 1, 2, 4, 6, and 8. Additional analyses included the change from baseline in the HAM-D depressed mood item at weeks 1, 2, 4, 6, and 8 and the change from baseline in the HAM-A, QOL, and CES-D at week 8.

RESULTS

Patient Characteristics

A total of 491 patients entered the double-blind treatment period: 119 in the escitalopram 10 mg/day group, 125 in the escitalopram 20 mg/day group, 125 in the citalopram 40 mg/day group, and 122 in the placebo group. These patients were included in all safety analyses. Efficacy was assessed in the intent-to-treat (ITT) population, which included all patients who had received at least 1 dose of double-blind study medication and had at least 1 postbaseline MADRS assessment. The ITT population consisted of 118 patients in the escitalopram 10 mg/day group, 123 in the escitalopram 20 mg/day group, 125 in the citalopram 40 mg/day group, and 119 in the placebo group.

Following randomization, there were no clinically meaningful differences between treatment groups on the basis of demography or disease severity, course, or duration at baseline (Table 1). The mean baseline scores across treatment groups are indicative of a patient sample with moderate-to-severe depressive symptomatology.

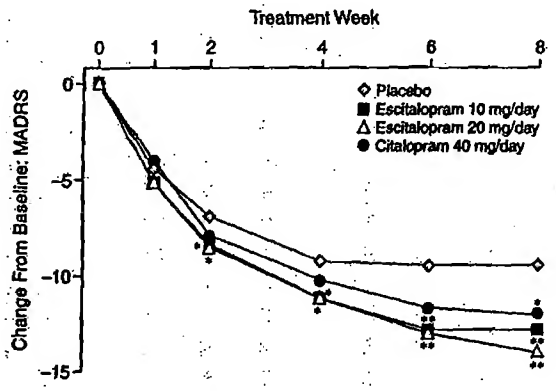
Efficacy

At study endpoint (week 8), the decreases from baseline in the MADRS, HAM-D, HAM-D depressed mood item, and CGI-S and the effect on the CGI-I for escitalopram, 10 mg/day, and escitalopram, 20 mg/day, were statistically significantly superior to those observed for placebo treatment. Citalopram, the active treatment control group, also produced significant improvement compared with placebo in all major efficacy variables (Table 2). Mean changes from baseline for the MADRS total score were −9.4, −12.8, −13.9, and −12.0 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. The change from baseline in MADRS total score was significantly associated with baseline MADRS score. Mean changes from baseline in the HAM-D total score were −7.6, −10.2, −11.7, and −9.9 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. It was of note that at least half of the patients in both the escitalopram 10 mg/day (50%) and escitalopram 20 mg/day (51.2%) treatment groups satisfied prospectively defined criteria for response to treatment (50% improvement in MADRS from baseline). The response rate in the citalopram 40 mg/day treatment group was 45.6%, and each of the 3 active treatment groups had statistically significantly greater response rates than placebo treatment (27.7%; $p < .01$, Cochran-Mantel-Haenszel test). Differences in response rate between each of the escitalopram dosage groups and the citalopram group were not significant.

There were no significant differences in the mean change from baseline to endpoint between the escitalopram 20 mg/day and citalopram 40 mg/day groups on the MADRS ($p = .09$) and the CGI-S ($p = .09$). It was of note that citalopram, 40 mg/day, was not more effective than escitalopram, 10 mg/day, on the majority of the major efficacy outcome variables at study endpoint, including MADRS, HAM-D, CGI-I, and CGI-S (Table 2).

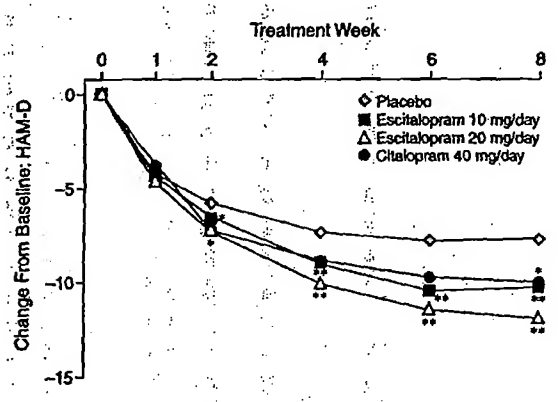
Analyses of patients completing 8 weeks of treatment (observed cases) were consistent with those for the LOCF analyses. At endpoint, the mean changes from baseline for the MADRS total score were −10.0, −14.0, −16.1, and −13.5 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. For the HAM-D total score, the mean changes at endpoint from

Figure 1. Mean Change From Baseline on the Montgomery-Asberg Depression Rating Scale in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



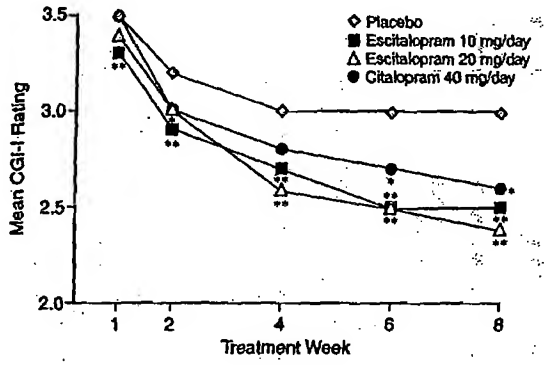
*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 2. Mean Change From Baseline on the Hamilton Rating Scale for Depression in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



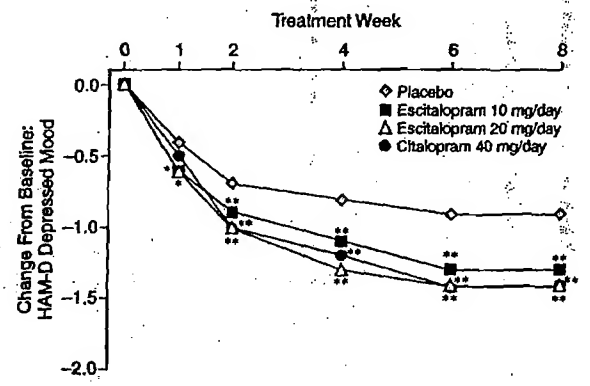
*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 3. Mean Clinical Global Impressions of Improvement Scores in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 4. Mean Change From Baseline on the Depressed Mood Item of the Hamilton Rating Scale for Depression in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



*p ≤ .05, compared with placebo.
**p ≤ .01, compared with placebo.

baseline were –8.2, –10.9, –13.3, and –11.0 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. For patients completing 8 weeks of treatment, each active treatment group was significantly different from placebo at endpoint. Differences between escitalopram 20 mg/day treatment and citalopram 40 mg/day treatment were not statistically significant on the observed cases analyses of either the MADRS total score (p = .07) or the HAM-D total score (p = .06).

A summary of efficacy results by study visit on the MADRS, HAM-D, CGI-I, and HAM-D depressed mood item is shown in Figures 1–4, respectively. On the MADRS (Figure 1) and HAM-D outcomes (Figure 2), statistically significant improvement compared with placebo treatment was observed with both escitalopram doses beginning 2 weeks after initiation of active treatment and continuing through every study visit to endpoint. On the CGI-I (Figure 3) and the HAM-D depressed mood item (Figure 4), escitalopram treatment significantly separated from placebo treatment after 1 week of double-blind treatment (immediately prior to up-titration in the escitalopram 20 mg/day group). These effects were maintained throughout the treatment period as well.

Additional analyses indicated that escitalopram effectively improved other aspects of depressive disorder. Anxiety symptoms, as measured with the HAM-A, were significantly reduced by escitalopram at endpoint. For the HAM-A, the difference in the mean change from baseline for escitalopram versus placebo treatment was –1.1 for the 10-mg/day group (p = .04) and –2.6 for the 20-mg/day

Table 3. Most Frequent Adverse Events (% of patients)[a]

Adverse Event	Placebo (N = 122)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 119)	Escitalopram 20 mg/d (N = 125)
Nausea	6	22	21	14
Diarrhea	7	11	10	14
Insomnia	3	11	10	14
Dry mouth	7	10	10	9
Ejaculatory disorder[b]	0	4	9	12

[a]Listed are those adverse events that occurred in at least 10% of patients in any active treatment group and were more prevalent than in the placebo treatment group.
[b]As a percentage of male patients; number of reports ranged from 2–5 per active treatment group.

group ($p < .01$). Both doses of escitalopram significantly improved scores on both patient-rated questionnaires used in this study. For the QOL, the difference in the mean change from baseline for escitalopram versus placebo treatment was 2.4 for the 10-mg/day group ($p = .04$) and 4.8 for the 20-mg/day group ($p < .01$). For the CES-D, the difference in the mean change from baseline for escitalopram versus placebo treatment was –2.7 for the 10-mg/day group ($p = .02$) and –6.8 for the 20-mg/day group ($p < .01$).

Six (4.9%) patients discontinued from the placebo treatment group for lack of efficacy, while only 3 (2.5%), 0, and 1 (0.8%) patients from the escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram treatment groups, respectively, discontinued for this reason.

Safety

Overall, 76% of patients completed the study. Completion rates were similar across all groups ($p = .73$, chi-square test).

Escitalopram was well tolerated in this study at both doses. Discontinuations due to adverse events occurred in 2.5% of placebo patients, 4.2% of escitalopram 10 mg/day patients, 10.4% of escitalopram 20 mg/day patients, and 8.8% of citalopram patients. There was no significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg/day group and the placebo group, but the differences were significant for both escitalopram, 20 mg/day, and citalopram, 40 mg/day ($p \leq .05$).

The rate of adverse events overall during the double-blind treatment period (treatment-emergent adverse events) did not differ between the escitalopram 10 mg/day group and the placebo group (79.0% vs. 70.5%; $p = .14$), although the rate of treatment-emergent adverse events was significantly different from placebo for both the escitalopram 20 mg/day group (85.6%; $p < .01$) and the citalopram 40 mg/day group (86.4%; $p < .01$).

The adverse events that occurred in at least 10% of patients in any active treatment group and were more prevalent than in the placebo treatment group were nausea, diarrhea, insomnia, dry mouth, and ejaculatory disorder (Table 3). The majority of these events were mild in severity. Noticeably absent from this list is somnolence, as well as symptoms of general activation (such as nervousness or anxiety), a finding that is consistent with previous clinical experience with the racemate.[10] Furthermore, reporting of sexual adverse events was low, with only ejaculatory disorder exceeding 10% in any active treatment group (Table 3). For example, anorgasmia was reported by 1% to 2% of patients in any group, and loss of libido was reported in 2% to 3% of patients in any active treatment group.

Analysis of laboratory, vital sign, body weight, and ECG parameters revealed no clinically remarkable changes from baseline.

DISCUSSION

This study provides strong clinical support for the antidepressant efficacy and tolerability of escitalopram at doses of 10 mg/day or higher. Furthermore, these results suggest that escitalopram within the doses studied may be more potent and better tolerated when administered as a single isomer than as a component of racemic citalopram.

Significant improvement relative to placebo treatment was observed in escitalopram-treated patients beginning in the first week of double-blind treatment, with significant differences being observed on the CGI-I and the HAM-D depressed mood item. By week 2, both escitalopram dose groups had significantly separated from placebo treatment on the MADRS and HAM-D. Although this study was not designed to evaluate the time to response, the rapidity with which escitalopram produced significant responses on all major efficacy parameters is consistent with its rapid onset of action in animal models.[14,16,24]

In addition to improving core depressive symptomatology, escitalopram treatment led to improvements over placebo in other aspects of depressive disorder, including anxiety, social functioning, and overall quality of life. The latter is of particular interest, since quality of life issues such as poor social functioning are often the impetus for depressed persons to seek treatment.[25] Anxiety is a common symptom in depression, affecting up to about 70% of depressed patients.[26] Comorbid anxiety is associated with increased disease severity.[9] In this regard, it is noteworthy that escitalopram significantly improved HAM-A scores as well.

Escitalopram was well tolerated; the rate of discontinuations for adverse events did not differ for the escitalopram 10 mg/day group and for placebo treatment (4.2% vs. 2.5%), and also did not differ for the escitalopram 20 mg/day group versus the citalopram 40 mg/day group (10.4% vs. 8.8%). Furthermore, the overall incidence of adverse events occurring during the double-blind treatment period did not differ between the escitalopram 10 mg/day group compared with placebo treatment (79.0% vs. 70.5%) and also did not differ for the escitalopram 20 mg/day group compared with the citalopram 40 mg/day group (85.6% vs. 86.4%). No adverse events occurred during escitalopram

treatment that were unexpected, given what is known from extensive clinical experience with citalopram.

There are a number of theoretical advantages to the development of single isomers of already approved racemic medications. Often the isomer that does not contribute to the therapeutic effects of the racemate nevertheless complicates the clinical response to the racemate.[6] Twice as much escitalopram is administered daily in the 40-mg/day citalopram dose than is administered in the 10-mg/day escitalopram dose, and one might expect from this that citalopram, 40 mg/day, would be more effective than escitalopram, 10 mg/day. This was not the case, however, since actual treatment with escitalopram, 10 mg/day, was at least as effective as citalopram, 40 mg/day, on the major efficacy outcome variables (MADRS, HAM-D, CGI-I, and CGI-S), as well as the MADRS response rate. These results raise the possibility that the presence of the *R*-enantiomer as a constituent of citalopram has a negative effect on the clinical efficacy seen with the racemate.

Another theoretical rationale for the clinical development of single isomer compounds is the avoidance of side effects associated with the opposite isomer. In comparison to 40 mg/day of citalopram, 10 mg/day of escitalopram was at least as well tolerated, in terms of individual adverse event rates, overall rates of treatment-emergent adverse events, and rates of discontinuation due to adverse events. In this study, therefore, escitalopram, 10 mg/day, provided at least as much antidepressant efficacy as citalopram, 40 mg/day, and with at least as favorable a tolerability profile. Since citalopram, 40 mg/day, is itself a routinely effective dose in clinical practice,[27] escitalopram, 10 mg/day, may be an adequate dose for routine practice as well.

Treatment with escitalopram, 20 mg/day, yielded further improvements in MADRS and HAM-D scores, but the differences relative to escitalopram, 10 mg/day, or citalopram, 40 mg/day, were not statistically significant. As this study was not designed to test differences between active treatment groups, it is not possible to draw firm conclusions; however, these results are certainly most encouraging and provide strong stimulus for further work to test the hypothesis that escitalopram provides greater antidepressant efficacy than citalopram.

These observations emphasize that an existing antidepressant compound can be improved upon by taking advantage of its chiral properties. In conclusion, escitalopram is a new, well-tolerated SSRI with antidepressant efficacy at the lowest tested dose of 10 mg/day.

Drug names: citalopram (Celexa), zolpidem (Ambien).

REFERENCES

1. Mendlewicz J, Lecrubier Y. Antidepressant selection: proceedings from a TCA/SSRI Consensus Conference. Acta Psychiatr Scand Suppl 2000;403: 5–8
2. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000;48: 894–901
3. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry 1995; 56:30–34
4. Joffe RT, Levitt AJ, Sokolov STH, et al. Response to an open trial of a second SSRI in major depression. J Clin Psychiatry 1996;57:114–115
5. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. J Clin Psychiatry 1997;58:16–21
6. Hutt AJ, Tan SC. Drug chirality and its clinical significance. Drugs 1996; 52:1–12
7. Tucker GT. Chiral switches. Lancet 2000;355:1085–1087
8. Willetts J, Lippa A, Beer B. Clinical development of citalopram. J Clin Psychopharmacol 1999;19:36S–46S
9. Joubert AF, Stein DJ. Citalopram and anxiety disorders. Rev Contemp Pharmacother 1999;10:79–123
10. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from US clinical trials. J Clin Psychiatry 2000;61:896–908
11. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–350
12. Hyttel J, Bøges KP, Perregaard J, et al. The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm Gen Sect 1992;88:157–160
13. Sanchez C, Brennum LT. The S-enantiomer of citalopram (Lu 26–054) is a highly selective and potent serotonin reuptake inhibitor. Presented at the 55th annual meeting of the Society of Biological Psychiatry; May 11–13, 2000; Chicago, Ill
14. Mitchell PJ, Hogg S. Behavioural effects of escitalopram predict potent antidepressant activity. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 9, 2001; New Orleans, La. Abstract NR503:136–137
15. Sanchez C, Hogg S. The antidepressant effect of citalopram resides in the S-enantiomer. Presented at the 40th annual meeting of the New Clinical Drug Evaluation Unit; May 30–June 2, 2000; Boca Raton, Fla
16. Montgomery SA, Loft H, Sanchez C, et al. Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. Pharmacol Toxicol 2001;88:282–286
17. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
18. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
20. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Helath; 1976:218–222
21. Hamilton M. Diagnosis and rating of anxiety. Br J Psychiatry 1969;Special publication:76–79
22. Weissman MM, Sholomskas D, Pottenger M, et al. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol 1977;106:203–214
23. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29: 321–326
24. Sanchez C. Escitalopram: potent anxiolytic effects in rodent models of anxiety. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 9, 2001; New Orleans, La. Abstract NR559:151
25. Hirschfeld RM, Montgomery SA, Keller MB, et al. Social functioning in depression: a review. J Clin Psychiatry 2000;61:268–275
26. Zimmerman M, McDermut W, Mattia JI. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. Am J Psychiatry 2000;157:1337–1340
27. Montgomery SA. Selecting the optimum therapeutic dose of serotonin reuptake inhibitors: studies with citalopram. Int Clin Psychopharmacol 1995;1:23–27

EXHIBIT B

ELSEVIER

Journal of Affective Disorders 54 (1999) 39–48

JOURNAL OF AFFECTIVE DISORDERS

Research report

A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder

Guy Chouinard[a,*], Bishan Saxena[b], Marie-Claire Bélanger[a], Arun Ravindran[c], David Bakish[c], Linda Beauclair[a], Paul Morris[d], N.P. Vasavan Nair[e], Rahul Manchanda[f], Robin Reesal[g], Ronald Remick[h], M. Colleen O'Neill[i]

[a]*Hôpital Louis-H. Lafontaine and Allan Memorial Institute, Montréal, Québec, Canada*
[b]*Hamilton Psychiatric Hospital, Hamilton, Ontario, Canada*
[c]*Royal Ottawa Hospital, Ottawa, Ontario, Canada*
[d]*Aberfoyle Clinic, Toronto, Ontario, Canada*
[e]*Douglas Hospital Research Centre, Verdun, Québec, Canada*
[f]*University Hospital, London, Ontario, Canada*
[g]*Western Behavioural Research Centre, Calgary, Alberta, Canada*
[h]*St. Paul's Hospital, Vancouver, British Columbia, Canada*
[i]*SmithKline Beecham Pharma, Oakville, Ontario, Canada*

Received 29 July 1997; received in revised form 25 May 1998; accepted 1 July 1998

Abstract

Background: Recent studies have suggested clinical differences among selective serotonin reuptake inhibitors. In a 12-week randomized, multicenter, double-blind trial, the antidepressant and anxiolytic efficacy of the selective serotonin reuptake inhibitors paroxetine and fluoxetine was compared in patients with moderate to severe depression.

Methods: A total of 203 patients were randomized to fixed doses (20 mg/day) of paroxetine or fluoxetine for the first six weeks of therapy. From week 7–12, dosing could be adjusted biweekly, as required (paroxetine 20–50 mg/day, and fluoxetine 20–80 mg/day). The mean prescribed doses were paroxetine 25.5 mg/day (range 20.0–40.2 mg/day), and fluoxetine 27.5 mg/day (range 20.0–59.5 mg/day). Emergence of motor nervousness or restlessness was assessed using the ESRS scale for akathisia.

Results: Both active treatments demonstrated comparable antidepressant efficacy (HAM-D, CGI). Anxiolytic activity of the two drugs (COVI, STAI, HAM-D) was also comparable. However, paroxetine was found to be superior to fluoxetine on two subscore measures at week 1 of therapy (HAM-D Agitation item, $p < 0.05$; Psychic Anxiety item, $p < 0.05$), with no differences detected after week 2. The overall incidence of adverse effects was comparable in the two treatment groups. Constipation, dyspepsia, tremor, sweating and abnormal ejaculation were more common in paroxetine-treated subjects, whereas nausea and nervousness were more frequent in fluoxetine-treated patients. Weight loss was more common in the fluoxetine versus paroxetine group (11.88% versus 2.94%, respectively). ESRS scores for akathisia were low throughout the study and showed little change.

*Corresponding author. Tel.: + 1-514-843-1672; Fax: + 1-514-843-8620.

0165-0327/99/$ – see front matter
PII: S0165-0327(98)00188-8

Limitations: Differences observed between the two drugs in antianxiety effects were limited to two measures of anxiety among several others.

Discussion: The data indicate that paroxetine and fluoxetine have comparable antidepressant and anxiolytic efficacy. Paroxetine appears to produce an earlier improvement in agitation and psychic anxiety symptoms compared with fluoxetine.

Keywords: Depression; Anxiety; Paroxetine; Fluoxetine; Antidepressant; SSRIs; Antianxiety

1. Introduction

Paroxetine and fluoxetine, both selective serotonin reuptake inhibitors (SSRIs), have been shown in randomized, placebo-controlled multicenter trials to be efficacious in the treatment of major depressive disorder (Bignamini and Rapisarda, 1992; Dunner et al., 1992; Mertens and Pintens, 1988; Chouinard, 1985; Noguera et al., 1991). The selectivity of SSRIs has been attributed to their relatively low affinity for cholinergic, histaminergic or catecholaminergic receptors (Thomas et al., 1987). Like other SSRIs, in clinical studies paroxetine was found to produce fewer undesirable cardiotoxic or anticholinergic adverse effects compared to tricyclic antidepressants (TCAs) and a lower propensity to cause sedation, hypotension, or dry mouth (Dunbar et al., 1991; Bascara, 1989; Cohn et al., 1990; Hutchinson et al., 1992). A recent meta-analysis of SSRIs indicates that this more favorable side effect profile results in a lower drug discontinuation rate than that seen with TCAs (Montgomery et al., 1994). Among SSRIs, paroxetine is thought to be the most anticholinergic, and has atropinic side effects that other SSRIs do not have (dry mouth, sedation, etc.).

SSRIs have the potential to produce transient excitatory side effects, which may be due to their interactions with other neurotransmitters, such as dopamine or norepinephrine (Tulloch and Johnson, 1992). SSRIs' interactions with dopaminergic neurotransmission have been most commonly reported with fluoxetine (Gardier et al., 1994; Leo, 1996), although evidence is mixed (Clark et al., 1996). Fluoxetine may induce extrapyramidal symptoms (EPS) such as akathisia (Lipinski et al., 1989; Leo, 1996) and dystonia (Leo, 1996), and may exacerbate parkinsonian symptoms in patients with Parkinson's Disease (Chouinard and Sultan, 1992; Leo, 1996); SSRI-induced EPS may be related to the agonist effect of serotonergic input to dopaminergic pathways (Leo, 1996). In addition, SSRIs have been associated with excitatory side effects including anxiety, nervousness and insomnia, which are reported to occur in up to 10–15% of fluoxetine-treated patients (Chouinard, 1985; product monograph, Prozac, 1996). An early induction of anxiety and agitation has been reported with fluoxetine (Gorman et al., 1987) and zimelidine (Huitfeldt and Montgomery, 1983), as well as with the tricyclic antidepressant imipramine (Zitrin et al., 1983).

Like other SSRIs, paroxetine has been found to alleviate comorbid anxiety and agitation symptoms in depressed patients (Sheehan et al., 1992). In comparative antidepressant clinical trials, paroxetine has been shown to produce an earlier improvement in concomitant anxiety symptoms compared with imipramine (Cohn and Wilcox, 1992) or fluoxetine (De Wilde et al., 1993).

The present study was designed to compare the antidepressant and anxiolytic efficacy of paroxetine and fluoxetine in patients with major depression, and to compare induction of nervousness and anxiety in the early stages of treatment.

2. Methodology

Eight Canadian centres enrolled 203 patients (78 men, 125 women, mean age 40.9 years) who met DSM-III-R criteria for major depressive disorder following a standard clinical interview by a psychiatrist (neither the SCID nor other structured clinical interviews were used). Patients were recruited through newspaper ads and referrals. Patients were included if they had symptoms of depression for at least one month prior to the screening visit, a total score of 20 on the 21-item Hamilton Depression

Rating Scale (HAM-D) (Hamilton, 1960), and a score of two on item one HAM-D at the screening visit (5–14 days prior to baseline) and at entry (Day 0). Patients were excluded if they had significant coexisting illness, including renal, hepatic, gastrointestinal, cardiovascular or neurological disease; non-stabilized diabetes; other current Axis I psychiatric diagnosis; organic brain syndrome; past or present abuse of alcohol or illicit drugs; were at significant risk of suicide; or were pregnant or lactating. Other exclusion criteria included ECT or continuous lithium therapy in the preceding two months, monoamine oxidase inhibitor or oral neuroleptic use in the preceding 21 days, any antidepressant or sedative hypnotic (except chloral hydrate) in the previous seven days, fluoxetine in the previous 35 days, or current therapy with an anticoagulant or type 1C antiarrhythmic (e.g. flecainide, propafenone). Patients who had clinically significant abnormalities on the prestudy physical examination, ECG or laboratory tests (hematology, biochemistry and thyroid tests) were also excluded. The use of formal psychotherapy was not permitted for the duration of the study.

The number of patients enrolled by site were 56 (Saxena, Hamilton); 40 (Ravindran, Ottawa); 29 (Morris, Etobicoke); 25 (Chouinard, Montreal); 22 (Nair, Montreal); 15 (Manchanda, London); 8 (Reesal, Calgary); and 8 (Remick, Vancouver). All patients were enrolled between December 13, 1991, and June 16, 1993. Demographic data are shown in Table 1.

Following a 5–14 day single-blind placebo washout period, subjects were randomized to receive

Table 1
Demographic data (randomized patients)

	Paroxetine (n = 102)	Fluoxetine (n = 101)
Men	37 (36.27%)	41 (40.59%)
Women	65 (63.73%)	60 (59.41%)
Mean age (years±SD)	40.6±10.71	41.2±10.71
Race:		
Caucasian	97 (95.1%)	99 (98.02%)
Asian	3 (2.94%)	1 (0.99%)
Other/Unknown	2 (1.96%)	1 (0.99%)
Number of previous depressive episodes		
1	24 (23.53%)	41 (40.59%)
2	19 (18.63%)	15 (14.85%)
3–4	12 (11.76%)	9 (8.91%)
5 +	8 (7.84%)	6 (5.94%)
Continuous (no specific MDE)	10 (9.80%)	2 (1.98%)
No previous episodes	29 (28.43%)	27 (26.73%)
Not specified	0 (0%)	1 (0.99%)
Duration of present MDE		
1–4 weeks	1 (0.98%)	1 (0.99%)
1–3 months	28 (27.45%)	29 (28.71%)
3–6 months	25 (24.51%)	22 (21.71%)
6–12 months	19 (18.63%)	19 (18.81%)
> 1 year	29 (28.43%)	30 (29.70%)
History of previous psychiatric disorders (confirmed or suspected)		
Alcoholism/drug abuse	11 (10.78%)	13 (12.87%)
Anxiety/obsessional disorders	15 (14.71%)	20 (19.80%)
Brief episodes of depression	40 (39.21%)	37 (36.63%)
Major episode of depression	72 (70.59%)	67 (66.34%)
Personality disorder	3 (2.94%)	6 (5.94%)
Suicide attempts	17 (16.67%)	13 (12.87%)
Other	4 (3.92%)	3 (2.97%)

paroxetine or fluoxetine for 12 weeks. Dosing for both active treatment groups was fixed at 20 mg/day for the first six weeks of therapy. From Week 7–12, dosing could be adjusted biweekly, as required, based on the patient's therapeutic response and tolerance of the medication as indicated by the efficacy index of the Clinical Global Impression (CGI) scale. The allowable dose ranges were paroxetine 20–50 mg/day, and fluoxetine 20–80 mg/day. Doses could be reduced to a minimum of 20 mg/day at any visit if an adverse event occurred. All benzodiazepines were excluded in this study because of the effects on the anxiety assessment. Choral hydrate as an hypnotic if required was the only permitted concomitant psychotropic therapy. Its use, however, was limited to the washout period and the first two weeks of active treatment.

Written informed consent was obtained from all patients prior to study entry. The study protocol and consent forms were approved by the individual centres' Institutional/Ethics Review Boards.

Patients were evaluated weekly for the first six weeks of the study, and at Week 8, 10 and 12. Response to treatment was defined as a $>50\%$ reduction in the HAM-D total score from baseline. Antidepressant efficacy was assessed using the HAM-D and CGI scales. The proportion of patients in each treatment group who showed a therapeutic response ($>50\%$ reduction from baseline in HAM-D score; and/or HAM-D total score <10) were also evaluated as efficacy measures. Anxiety was measured with the Covi Anxiety scale and the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970); anxiogenesis of the akathisic type was investigated with the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al., 1980).

Secondary efficacy measures included the HAM-D anxiety/somatization factor score, and HAM-D anxiety items (Agitation, Psychic Anxiety, Somatic Anxiety).

The emergence of anxiety was assessed at two time periods: early in therapy (weeks 1–2), and for the entire study period (weeks 1–12). Patients who had baseline scores of zero on the HAM-D agitation, somatic and psychic anxiety items, and who subsequently developed scores >0 were considered to have emergent new anxiety symptoms.

Safety was assessed through monitoring of adverse experiences, vital signs and clinical laboratory data. This analysis was performed on the intent-to-treat data.

2.1. Statistical methodology

Two patient samples were considered for analysis: intent-to-treat (ITT) (all patients randomized to study medication), and per-protocol (exclusion of all major protocol violators). Since there were few major protocol violators ($n=8$), the per-protocol analysis was only performed on the primary efficacy parameters to ensure consistency with the ITT results. The efficacy analysis included all randomized patients who underwent at least one on-therapy efficacy evaluation (paroxetine, $n=100$; fluoxetine, $n=98$).

Two data sets were used to analyze the efficacy data: observed cases, and last-observation-carried-forward (LOCF) endpoint.

Hypothesis tests for the three types of data analyzed in this study were performed using the SAS system version 6.07 statistical software.

1. Proportional data, such as the proportion of patients achieving a dichotomous efficacy response, were analyzed using a generalized logit methodology via the Categorical Model (CATMOD) procedure of the SAS system. Weighted least squares parameter estimations were used for effects of treatment, investigator and interaction. A test of investigator by treatment interaction was made, and if a significant interaction existed ($p \leq 0.10$), its type and nature were investigated further and the data were reviewed to decide whether pooling over centres was justified. The statistical model determined for the endpoint analysis was then used for analyzing the early-week visit data. Ninety-five percent confidence intervals were calculated.

2. Parameters considered as continuous variables, such as baseline mean scores and change from baseline scores of efficacy scales, were analyzed using parametric analysis of variance methodology. The General Linear Models (GLM) procedure of the SAS system was used to perform the analysis. Ninety-five percent confidence intervals were calculated.

The mean change from baseline at endpoint for each of the efficacy parameters was analyzed using a model with effects for treatment, investigator and interaction. If the treatment effects varied significantly among the investigators (p value of inter-

action ≤ 0.10), the data were evaluated to assess the nature of the interaction. After the initial statistical model had been determined, the mean change from baseline at each visit was assessed using the model determined from the endpoint analysis. For the CGI-Global Improvement data, baseline assessments were not made. Therefore, raw scores were tested using the GLM procedure.

Comparability of means at baseline for the HAM-D total, HAM-D anxiety items, HAM-D anxiety/somatization factor, CGI-Severity of Illness, COVI, STAI, and ESRS were tested using the GLM procedure of SAS with effects for treatment and investigator. If the treatment effect was significant at alpha = 0.05, then the baseline value was used as a covariant in the model for that efficacy variable for all subsequent analyses.

A post-hoc stratification of patients was performed on the baseline COVI score. Patients with a score of seven were classified as anxious; those with scores <7 were classified as non-anxious. Analysis of variance was again performed on the HAM-D total score data using a model with effects for treatment, COVI factor, and treatment by factor.

3. For categorical data, a Fisher's Exact test was used for 2X2 tables. Fisher's Exact tests were performed to compare the two treatments with regard to the emergence of anxiety on the individual anxiety items of the HAM-D.

Tests of significance concerning interaction terms were considered significant if the p values were ≤ 0.10. Tests of hypothesis concerning the significance of overall treatment effects were considered significant if the p values were ≤ 0.05.

3. Results

A total of 203 patients were randomized and 130 patients (64.04%) completed the study (Table 2). The proportion of patients who failed to complete the 12-week trial was comparable between the two active treatment groups (paroxetine 39.22%, fluoxetine 32.67%). Reasons for premature withdrawal included lack of efficacy/relapse, adverse experiences, lack of patient compliance, loss of patient to follow-up, patient improvement, and protocol violations.

A total of 100 patients in the paroxetine group and 98 patients in the fluoxetine group were evaluable for the LOCF endpoint analysis. The mean prescribed doses were paroxetine 25.5 mg/day (range 20.0–40.2 mg/day), and fluoxetine 27.5 mg/day (range 20.0–59.5 mg/day). Patient compliance with medications, assessed using pill counts, was $>90\%$ in both treatment groups.

3.1. Efficacy analysis

Both active treatments produced comparable improvements in HAM-D total scores from baseline at each of the observed time points (Table 3). At week 12, the mean decline in HAM-D total score was 17.80 for paroxetine, and 18.46 for fluoxetine. The overall treatment response was similar for both

Table 3
Mean change (±S.D.) from baseline in HAM-D total score (21 items): observed cases and LOCF endpoint ($n = 198$)

Week	Paroxetine	Fluoxetine	P value
Baseline	25.91±0.46	25.45±0.46	0.425
1	−4.21±0.63	−3.99±0.63	0.777
2	−8.58±0.74	−7.40±0.73	0.208
3	−10.36±0.82	−11.37±0.81	0.330
4	−11.47±0.82	−11.75±0.80	0.786
5	−13.51±0.81	−12.79±0.80	0.479
6	−14.67±0.89	−14.47±0.85	0.860
8	−15.59±0.92	−14.77±0.86	0.469
10	−16.35±0.96	−16.97±0.91	0.598
12	−17.80±0.99	−18.46±0.91	0.584
Endpoint	−13.92±1.10	−14.78±1.10	0.538

Table 2
Reasons for premature withdrawal

	Paroxetine ($n = 102$)	Fluoxetine ($n = 101$)
Completed study	62	68
Withdrawn due to adverse event and/or lack of efficacy	22 (21.57%)	25 (24.75%)
Withdrawn due to any reason	40 (39.22%)	33 (32.67%)

treatment groups, with the greatest proportion of responders found at week 12. Using the criterion of >50% reduction in HAM-D total score from baseline, 85.7% (67% endpoint) of paroxetine-treated patients and 88.4% (68.4% endpoint) of fluoxetine-treated patients responded (Table 4). For the criterion of HAM-D score <10, the response rates were 77.8% (58% endpoint) with paroxetine and 81.2% (59.2% endopoint) with fluoxetine (Table 5). There were no statistically significant treatment effects for either of the response criteria.

In assessing the mean change in CGI-Severity of Illness scores, there was greater improvement ($p = 0.05$) at week 2 with paroxetine (−0.67) versus fluoxetine (−0.44) (Table 6). At all other time points, the mean CGI-Severity of Illness scores were comparable for both treatment groups. The effect of gender on efficacy or anxiety ratings was not investigated in this study.

3.2. Secondary efficacy parameters

Both paroxetine and fluoxetine produced comparable improvements in anxiety. Scores obtained on the Covi Anxiety Scale and the patient-rated STAI demonstrated progressive decreases in anxiety with both medications throughout the course of the trial.

Improvements in the HAM-D Anxiety/Somatization factor, comprising items 10 (psychic anxiety), 11 (somatic anxiety), 12 (somatic symptoms), 13 (general somatic symptoms), 15 (hypochondriasis)

Table 4
Number (%) of patients responding to treatment; response defined as >50% reduction in HAM-D total score from baseline: observed cases and LOCF endpoint ($n = 198$)

Week	Paroxetine (%)	Fluoxetine (%)	p value
1	9/99 (9.1)	6/98 (6.1)	0.632
2	29/88 (33.0)	25/92 (27.2)	0.359
3	37/86 (43.0)	43/86 (50.0)	0.341
4	40/84 (47.6)	50/85 (58.8)	0.125
5	55/80 (68.8)	50/81 (61.7)	0.435
6	55/77 (71.4)	54/80 (67.5)	0.684
8	51/73 (69.9)	53/75 (70.7)	0.988
10	51/70 (72.9)	59/70 (84.3)	0.178
12	54/63 (85.7)	61/69 (88.4)	0.952
Endpoint	67/100 (67.0)	67/98 (68.4)	0.927

Table 5
Number (%) of patients responding to treatment; response defined as HAM-D total score <10: observed cases and LOCF endpoint ($n = 198$)

Week	Paroxetine (%)	Fluoxetine (%)	p value
1	7/99 (7.1)	4/98 (4.1)	0.555
2	15/88 (17.0)	11/92 (12.0)	0.311
3	26/86 (30.2)	29/86 (33.7)	0.755
4	31/84 (36.9)	35/85 (41.2)	0.540
5	40/80 (50.0)	40/81(49.4)	0.983
6	40/77 (51.9)	44/80 (55.0)	0.682
8	40/73 (54.8)	46/75 (61.3)	0.509
10	42/70 (60.0)	51/70 (72.9)	0.181
12	49/63 (77.8)	56/69 (81.2)	0.889
Endpoint	58/100 (58.0)	58/98 (59.2)	0.837

Table 6
Mean change (±S.D.) from baseline in CGI Severity of Illness scores: observed cases and LOCF endpoint ($n = 198$)

Week	Paroxetine	Fluoxetine	p value
Baseline	4.25±0.07	4.14±0.07	0.199
1	−0.28±0.07	−0.19±0.07	0.322
2	−0.67±0.09[a]	−0.44±0.09	0.051[a]
3	−0.95±0.12	−1.01±0.12	0.702
4	−1.10±0.13	−1.00±0.12	0.526
5	−1.30±0.14	−1.28±0.14	0.902
6	−1.60±0.14	−1.63±0.13	0.821
8	−1.73±0.15	−1.72±0.14	0.995
10	−1.95±0.15	−2.06±0.15	0.549
12	−2.32±0.15	−2.42±0.14	0.616
Endpoint	−1.69±0.16	−1.80±0.16	0.595

[a] $p = -0.05$ (trend in favor of paroxetine).

Table 8
Mean change (±SD) from baseline in the HAM-D Psychic Anxiety item: observed cases and LOCF endpoint ($n = 198$).

Week	Paroxetine	Fluoxetine	p value
Baseline	2.34±0.08	2.34±0.08	0.997
1	−0.44±0.10[a]	−0.19±0.10	0.045[a]
2	−0.75±0.11	−0.58±0.10	0.208
3	−0.91±0.12	−0.89±0.12	0.856
4	−0.97±0.12	−1.04±0.12	0.642
5	−1.18±0.13	−1.02±0.13	0.310
6	−1.36±0.13	−1.37±0.12	0.957
8	−1.18±0.14	−1.11±0.13	0.676
10	−1.30±0.15	−1.37±0.14	0.679
12	−1.53±0.15	−1.64±0.14	0.547
Endpoint	−1.17±0.14	−1.21±0.14	0.823

[a] $p < 0.05$ Significant difference, paroxetine versus fluoxetine, in favor of paroxetine.

and 17 (insight), were comparable in the two treatment groups.

The mean change from baseline was also assessed on HAM-D individual items. There were significant treatment differences in favor of paroxetine on both the HAM-D agitation ($p = 0.032$) and psychic anxiety ($p = 0.045$) items at week 1 of treatment (Table 7, Table 8).

Objective and subjective ratings of restlessness were obtained using the akathisia items of the ESRS. The mean baseline values on both the objective and subjective items were less than one for both treatment groups, indicating a low incidence of akathisia prior to treatment. Mean objective ESRS akathisia scores declined throughout the course of the study with both active treatments. Similarly, subjective akathisia scores showed a general decline. At week 1, mean subjective ESRS akathisia scores declined from baseline in the paroxetine-treated group (−0.04), but increased in fluoxetine-treated subjects (+0.05). This trend did not reach statistical significance.

Table 7
Mean change (±SD) from baseline in the HAM-D Agitation item: observed cases and LOCF endpoint ($n = 198$)

Week	Paroxetine	Fluoxetine	p value
Baseline	0.81±0.07	0.74±0.07	0.442
1	−0.29±0.07[a]	−0.09±0.07	0.032[a]
2	−0.33±0.08	−0.18±0.08	0.159
3	−0.44±0.09	−0.38±0.09	0.585
4	−0.35±0.08	−0.37±0.08	0.878
5	−0.45±0.08	−0.40±0.08	0.654
6	−0.52±0.08	−0.49±0.08	0.721
8	−0.56±0.10	−0.43±0.09	0.284
10	−0.43±0.09	−0.55±0.08	0.278
12	−0.47±0.09	−0.54±0.09	0.554
Endpoint	−0.40±0.08	−0.39±0.08	0.978

[a] $p < 0.05$ Significant difference, paroxetine versus fluoxetine, in favor of paroxetine.

3.3. Emergent anxiety

The emergence of new anxiety symptoms was assessed early in therapy (week 1 and 2) and across the entire study period (week 1 to 12) using scores on the HAM-D agitation, psychic and somatic anxiety items in patients with baseline scores of zero. Eleven percent of patients in the paroxetine group and 12.2% of patients in the fluoxetine group experienced emergent new agitation. Of these, 6.1% and 9.2% with paroxetine and fluoxetine, respectively, occurred in the first two weeks of treatment. For somatic anxiety, 7.0% and 4.1% of paroxetine- and fluoxetine-treated patients, respectively, experienced emergent new somatic anxiety. Treatment differences were not statistically significant. Three patients in the paroxetine group reported emergent new psychic anxiety symptoms, but no fluoxetine-treated patients did.

3.4. Adverse events

Adverse events analyses comprised all 203 patients randomized to study medication. The incidence of adverse events was similar in the two treatment groups. There were 15 clinically significant adverse events during the course of the study. Three patients were hospitalized for medical reasons unrelated to the medications and one of them was withdrawn from the study. Four paroxetine- and two fluoxetine-treated patients were withdrawn for psychiatric reasons. In the paroxetine group, the psychiatric reasons for withdrawal were: severe anxiety and moderate agitation ($n = 1$); insomnia and depression ($n = 1$); suicidal ideation with a definite suicidal plan ($n = 1$); and increased suicidal tendencies and deterioration of depression ($n = 1$). In the fluoxetine group, the psychiatric reason for withdrawal was for suicidal tendencies ($n = 2$).

In addition, six patients experienced significantly disabling or incapacitating adverse effects. In the paroxetine group ($n = 3$), the disabling/incapacitating effects were: depersonalization, constipation, impaired concentration, dizziness and abnormal vision ($n = 1$); pharyngitis ($n = 1$); and suspected hypomania ($n = 1$). Two of these patients (depersonalization, suspected hypomania) were withdrawn. In the fluoxetine group ($n = 3$), the disabling/incapacitating effects were: rash/pruritus with tachycardia ($n = 1$); multiple nosebleeds ($n = 1$); and elevated TSH and detection of microsomal antibodies ($n = 1$). Two of these patients (rash/pruritus, multiple nosebleeds) were withdrawn from the study.

The most common adverse events were nausea, headache, and insomnia (Table 9). The reported rates of constipation, dyspepsia, tremor, sweating and abnormal ejaculation were higher among paroxetine-treated subjects. The incidence of diarrhoea was higher in the fluoxetine group.

The incidence of drop-out due to individual adverse events was generally below 5% for both treatment groups. Eight fluoxetine-treated patients (7.92%) were withdrawn due to nausea compared with four (3.92%) paroxetine-treated patients. In addition, 6.93% of fluoxetine-treated patients were withdrawn due to emergent nervousness compared with 1.96% of paroxetine-treated patients. Conversely, more patients in the paroxetine group were withdrawn due to insomnia (paroxetine: 5.88%; fluoxetine: 1.98%) and abnormal ejaculation (paroxetine: 5.41%; fluoxetine: 0.0%).

Table 9
Number of patients (%) with an incidence (> 10%) of adverse events ($n = 203$)

Preferred term	Paroxetine (%)	Fluoxetine (%)
Nausea	38 (37.25)	32 (31.68)
Headache	37 (36.27)	37 (36.63)
Insomnia	27 (26.47)	23 (22.77)
Abnormal ejaculation†	(24.32)	5 (12.20)
Somnolence	19 (18.63)	17 (16.83)
Constipation	18 (17.65)	4 (3.96)
Nervousness	14 (15.69)	16 (15.84)
Dry mouth	15 (14.71)	17 (16.83)
Tremor	14 (13.73)	7 (6.93)
Sweating	14 (13.73)	6 (5.94)
Agitation	13 (12.75)	10 (9.90)
Respiratory disorder	13 (12.75)	9 (8.91)
Dyspepsia	13 (12.75)	6 (5.94)
Diarrhea	12 (11.76)	19 (18.81)
Asthenia	12 (11.76)	10 (9.90)
Impotence [a]	4 (10.81)	3 (7.32)

[a] Corrected for gender.

There were no significant changes in vital signs with either medication. One patient in the paroxetine group experienced a transient increase in pulse rate, but this was not attributed to the medication. A comparable proportion of patients in each treatment group experienced weight gain (paroxetine: 10.78%; fluoxetine: 13.86%). Weight loss was more common in the fluoxetine versus paroxetine group (11.88% versus 2.94%, respectively).

4. Discussion

The present 12-week study compared the efficacy and tolerability of two selective serotonin reuptake inhibitors, paroxetine and fluoxetine, in reducing symptoms of depression and anxiety in 203 patients with moderate depression. Both medications had comparable efficacy in improving depressive symptoms, as assessed by declines in HAM-D total score from baseline. At the end of the 12-week trial, two-thirds of patients in each treatment group responded (> 50% decline from baseline in HAM-D total score).

Both study medications produced comparable

improvement in anxiety symptoms by the end of the study. However, paroxetine was found to produce an earlier improvement in agitation and psychic anxiety by week 1 of therapy compared with fluoxetine, which may be explained by differences in time to steady-state concentration (7–14 days for paroxetine versus 28–35 days with fluoxetine).

Similar results have been reported by other investigators. A pooled analysis (Dunbar and Fuell, 1990) of paroxetine-treated patients found that paroxetine was superior to active controls in alleviating agitation and psychic anxiety symptoms at week 4 of therapy. Similarly, a study in depressed outpatients (Dunbar et al., 1991) reported a small but significant difference in HAM-D Anxiety/Somatization scores in favor of paroxetine versus imipramine.

In addition, a number of studies have suggested that paroxetine may have a slightly more rapid onset of action than fluoxetine. A six-week study of 100 depressed patients demonstrated a statistical advantage of paroxetine over fluoxetine at week 3 of therapy (De Wilde et al., 1993). A study of 106 geriatric patients with depression also found a significantly greater improvement in HAM-D total scores at Week 3 of treatment with paroxetine compared with fluoxetine (Schöne and Ludwig, 1993). A similar trend was reported by Tignol in a multicenter comparison of paroxetine and fluoxetine (Tignol, 1993).

In contrast, there were more paroxetine patients ($n = 3$) with emergent new psychic anxiety symptoms (HAM-D psychic anxiety item) during the first two weeks of treatment in patients with baseline scores of zero, perhaps a result of paroxetine's shorter half-life (19 h versus 45–72 h for fluoxetine), which would allow rebound new symptoms to emerge before steady state is achieved in paroxetine-treated patients.

Emergence of motor nervousness or restlessness was assessed using the ESRS scale for akathisia. It is noteworthy that ESRS scores for akathisia were low throughout the study and showed little change (a trend in favor of paroxetine), suggesting that symptoms of anxiety and nervousness in depressed patients were not extrapyramidal in nature. We suggest that the induction of EPS symptoms by SSRIs occurs in patients with pre-existing detected or undetected neurological disorder and/or with dopaminergic dysfunction induced by antipsychotic drugs (Chouinard and Sultan, 1992).

There were no differences between paroxetine (P) and fluoxetine (F) that would appear to be secondary to prior medication withdrawal. At the time of enrollment, no significant differences between the two groups in medications being taken for the current episode. Medications included TCAs (P: 22.55%; F: 25.74%), SSRIs (P: 13.73%; F: 4.95%), and benzodiazepines (P: 26.47%; F: 22.77%). All current psychotropic medications were discontinued prior to the start of the trial and were not permitted for the duration of the study.

Both medications were generally well tolerated. Adverse effects were most commonly serotonergic and included nausea, headache and insomnia. Constipation, dyspepsia, tremor, sweating and abnormal ejaculation were more common in paroxetine-treated subjects, whereas nausea and nervousness were more frequent in fluoxetine-treated patients. The incidence of adverse events was comparable to that reported in the literature (Boyer and Feighner, 1991; Boyer and Blumhardt, 1992).

In conclusion, paroxetine and fluoxetine were found to have comparable efficacy in the treatment of major depression. Paroxetine appears to produce an earlier onset of anxiolytic effect than fluoxetine, but this result needs to be interpreted in the context of multiple comparisons and prior similar results in the published literature.

References

Bascara, L., 1989. A double-blind study to compare the effectiveness and tolerability of paroxetine and amitriptyline in depressed patients. Curr Ther Res 46, 815–820.

Bignamini, A., Rapisarda, V., 1992. A double-blind multicentre study of paroxetine and amitriptyline in depressed outpatients (Italian paroxetine study group). Int Clin Psychopharmacol 6 (suppl 4), 37–41.

Boyer, W.F., Blumhardt, C.L., 1992. The safety profile of paroxetine. J Clin Psychiatry 2 (suppl), 61–66.

Boyer, W.F., Feighner, J.P., 1991. Side effects of the selective serotonin reuptake inhibitors. In: Feighner, J.P., Boyer, W.F., (Eds). Selective Serotonin Reuptake Inhibitors. John Wiley and Sons, Chichester, U.K., pp. 133–152.

Chouinard, G., Ross-Chouinard, A., Annable, L., Mercier, P., 1980. The extrapyramidal symptom rating scale. Can J Neurol Sci 7, 233.

Chouinard, G., Sultan, S., 1992. A case of Parkinson's disease exacerbated by fluoxetine. Human Psychopharmacol 7, 63–66.

Chouinard, G., 1985. A double-blind controlled clinical trial of fluoxetine and amitriptyline in the treatment of outpatients with major depressive disorder. J Clin Psychiatry 47, 32–37.

Clark, R.N., Ashby, Jr. C.R., Dewey, S.L., Ramachandran, P.V., Strecker, R.E., 1996. Effect of acute and chronic fluoxetine on extracellular dopamine levels in the caudate-putamen and nucleus accumbens of rat. Synapse 23, 125–131.

Cohn, J.B., Wilcox, C.S., 1992. Paroxetine in major depression: a double-blind trial with imipramine and placebo. J Clin Psychiatry 53 (2, suppl), 52–56.

Cohn, J.B., Crowder, J.E., Wilcox, C.S., Ryan, P.J., 1990. A placebo and imipramine controlled study of paroxetine. Psychopharmacol Bull 26, 185–189.

De Wilde, J., Spiers, R., Mertens, C., Bartholomé, F., Schotte, G., Leyman, S., 1993. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand 87, 141–145.

Dunbar, G.C., Fuell, D.L., 1990. The anti-anxiety and anti-agitation effects of paroxetine in depressed patients. Int Clin Psychopharmacol 6 (suppl 4), 81–90.

Dunbar, G.C., Cohn, J.B., Fabre, L.F., Feighner, J.P., Fieve, R.R., Mendels, J., Shrivastava, R.K., 1991. A comparison of paroxetine, imipramine and placebo in depressed out-patients. Br J Psychiatry 159, 394–398.

Dunner, D.L., Cohn, J.B., Walshe, III T., Cohn, C.K., Feighner, J.P., Fieve, R.R., Halikas, J.P., Hartford, J.T., Hearst, E.D., Settle, Jr. E.C., Menolascino, F.J., Muller, D.J., 1992. Two combined, multicenter double-blind studies of paroxetine and doxepin in geriatric patients with major depression. J Clin Psychiatry 53 (suppl), 57–60.

Gardier, A.M., Lepoul, E., Trouvin, J.H., Chanut, E., Dessalles, M.C., Jacquot, C., 1994. Changes in dopamine metabolism in rat forebrain regions after cessation of long-term fluoxetine treatment: relationship with brain concentrations of fluoxetine and norfluoxetine. Life Sci 54, PL51–56.

Gorman, J.M., Liebowitz, M.R., Fyer, A.J., Goetz, D., Campeas, R.B., Fyer, M.R., Davies, S.O., Klein, D.F., 1987. An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 7, 329–332.

Hamilton, M., 1960. A rating scale for depression. J Neurosurg Psychiatry 12, 56–62.

Huitfeldt, B., Montgomery, S.A., 1983. Comparison between zimelidine and amitriptyline of efficacy and adverse symptoms. Acta Psychiatr Scand 69 (suppl 308), 55–69.

Hutchinson, D.R., Tong, S., Moon, C.A., Vince, M., Clarke, A., 1992. Paroxetine in the treatment of elderly depressed patients in general practice: a double-blind comparison with amitriptyline. Int Clin Psychopharmacol 6 (suppl 4), 43–51.

Leo, R.J., 1996. Movement disorders associated with the serotonin reuptake inhibitors. J Clin Psychiatry 57, 449–454.

Lipinski, Jr. J.F., Mallya, G., Zimmerman, P., Pope, Jr. H.G., 1989. Fluoxetine-induced akathisia: clinical and theoretical implications. J Clin Psychiatry 50, 339–342.

Mertens, C., Pintens, H., 1988. Paroxetine in the treatment of depression. A double-blind multicenter study versus mianserin. Acta Psychiatr Scand 77, 683–688.

Montgomery, S.A., Henry, J., McDonald, G., Dinan, T., Lader, M., Hindmarch, I., Clare, A., Nutt, D., 1994. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. Int Clin Psychopharmacol 9, 47–53.

Noguera, R., Altuna, R., Alvarez, E., Ayuso, J.L., Casais, L., Udina, C., 1991. Fluoxetine versus clomipramine in depressed patients: a controlled multicentre trial. J Affect Disord 22, 119–124.

Prozac (fluoxetine) product monograph, 1996. Eli Lilly and Co., Indianapolis, Indiana.

Schöne, W., Ludwig, M., 1993. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. J Clin Psychopharmacol 13 (suppl 2), 34S–39S.

Sheehan, D., Dunbar, G.C., Fuell, D.L., 1992. The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacol Bull 28, 139–143.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. The State-Trait Anxiety Inventory Test manual. Consulting Psychologists Press, Palo Alto, CA.

Thomas, D.R., Nelson, D.R., Johnson, A.M., 1987. Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor. Psychopharmacology 93, 193–200.

Tignol, J., 1993. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. J Clin Psychopharmacol 13 (6, suppl 2), 18S–22S.

Tulloch, I.F., Johnson, A.M., 1992. The pharmacologic profile of paroxetine, a new selective serotonin reuptake inhibitor. J Clin Psychiatry 53 (2, suppl), 7–12.

Zitrin, C.M., Klein, D.F., Woerner, M.G., Ross, D.C., 1983. Treatment of phobias. I: Comparison of imipramine hydrochloride and placebo. Arch Gen Psychiatry 40, 125–138.

EXHIBIT C

A Multicenter Evaluation of the Efficacy and Safety of 150 and 300 mg/d Sustained-Release Bupropion Tablets Versus Placebo in Depressed Outpatients

Frederick W. Reimherr, MD,[1] Lynn A. Cunningham, MD,[2] Sharyn R. Batey, PharmD,[3] J. Andrew Johnston, PharmD,[3] and John A. Ascher, MD[3]

[1]University of Utah Medical Center, Salt Lake City, Utah, [2]Clinical Research Associates, Edwardsville, Illinois, and [3]Glaxo Wellcome Inc., Research Triangle Park, North Carolina

ABSTRACT

This multicenter, randomized, double-masked, placebo-controlled, parallel-group study compared the antidepressant efficacy and safety of bupropion sustained-release (SR) tablets (150 mg QD or 150 mg BID) with placebo in outpatients with moderate-to-severe depression. The study consisted of a 1-week placebo phase followed by 8 weeks of active treatment with bupropion SR 150 mg/d (150 mg QD, n = 121) or 300 mg/d (150 mg BID, n = 120) or placebo (n = 121). Efficacy was measured by changes in scores on the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions for Severity of Illness (CGI-S) and Clinical Global Impressions for Improvement of Illness (CGI-I) scales. Safety was monitored by regular assessment of vital signs and adverse events as well as by pretreatment and posttreatment physical and clinical laboratory examinations. By day 56, both bupropion SR treatments were more effective in relieving the symptoms of depression than was placebo. Compared with those receiving placebo, patients in the bupropion SR 150- and 300-mg/d groups had significantly reduced symptoms by treatment day 56, as measured on the 17-item HAM-D, CGI-S, and CGI-I scales ($P < 0.05$). Bupropion SR was well tolerated, with no serious adverse events reported by bupropion-treated patients; 95% of all reported adverse events were of mild or moderate intensity. No clinically significant changes in vital signs, laboratory test results, or physical findings were observed. A greater mean weight loss was observed at the end of treatment in both the bupropion SR 150-mg (0.5 kg) and bupropion SR 300-mg (1.0 kg) group compared with placebo (0.2 kg). We found that bupropion SR 150 mg administered either once or twice daily was more effective than placebo in treating depression and that once-daily dosing appears to be at least as effective as twice-daily dosing. Should this prove true, de-

0149-2918/98/$19.00

pressed patients may be able to benefit from the convenience and improved tolerability associated with once-daily dosing. ***Key words:*** bupropion, depression, antidepressants, sustained-release.

INTRODUCTION

With a lifetime prevalence of nearly 6% in the United States,[1] depression poses diagnostic and therapeutic challenges for clinicians. The diagnosis of depression is frequently confounded by a variety of somatic complaints such as sleep disturbance, headache, gastrointestinal upset, and fatigue; the variability and cyclic nature of depressive symptoms; and the frequent co-occurrence of other chronic illnesses.[2,3] Because the treatment of depression is continuously evolving as new therapeutic options are introduced, it is important that physicians be thoroughly informed about the available medications.

Bupropion hydrochloride,* a unique aminoketone antidepressant, has been shown to be well tolerated and effective.[4–8] It is chemically unrelated to other known antidepressant agents (eg, the tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], and monoamine oxidase inhibitors [MAOIs]). Bupropion affects noradrenergic and/or dopaminergic but not serotoninergic function and has no known affinity for postsynaptic receptors.[9,10] It has not been reported to possess anticholinergic, cardiotoxic, antihistaminic, antiserotoninergic, or sedating properties.[11–13]

Bupropion has been available in the United States in an immediate-release (IR) formulation since 1989 and in a sustained-release (SR) formulation since 1996. Bupropion SR was developed to provide lower peak plasma levels than the IR formulation and to allow twice-daily administration. The bioequivalence of the SR and IR formulations has been demonstrated in clinical studies.[14] Peak plasma concentrations of drug after single doses of bupropion SR are approximately 50% lower than after equal doses of bupropion IR. Single-dose peak plasma concentrations of the three detectable metabolites of bupropion are equivalent after equal doses of bupropion SR and bupropion IR (unpublished data, Glaxo Wellcome Inc., 1998). The present study was undertaken to evaluate the efficacy and safety of bupropion SR 150 mg administered once or twice daily versus placebo.

PATIENTS AND METHODS

Patients

Eligible patients were males and females ≥18 years of age with a DSM III-R[15] (*Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised) diagnosis of major depression (single or recurrent episode) and a minimum score of 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[16,17] who presented with a major depressive episode of at least 4 weeks' but less than 2 years' duration. Exclusions were a known predisposition to seizures (including febrile seizure during childhood, epilepsy, brain tumor, significant head trauma, family history of idiopathic seizure disorder, or current treatment with medications that lower the seizure threshold), a history of unresponsiveness to pharmacotherapy for depression, a history or current diagnosis of

*Trademark: Wellbutrin® (Glaxo Wellcome Inc., Research Triangle Park, North Carolina).

anorexia nervosa or bulimia, a history of alcohol or substance abuse within 1 year prior to the study, or active suicidal behavior or ideation. Pregnant or lactating women and women not using an acceptable form of contraception were also excluded. Patients could not have received any psychoactive drug within 1 week of the treatment phase (2 weeks for MAOIs or protriptyline, 4 weeks for fluoxetine or any investigational drug).

Study Design

This multicenter, randomized, double-masked, placebo-controlled, parallel-group study consisted of a 1-week, single-masked placebo phase followed by an 8-week double-masked treatment phase. The study protocol was approved by the institutional review board for each of the six study sites, and written informed consent was obtained from each patient.

During an initial screening visit, medical and psychiatric histories were taken and physical examinations, clinical laboratory tests, psychiatric evaluations, and, if clinically indicated, a standard 12-lead electrocardiogram (ECG) were performed. Patients entered in the placebo phase of the study received one placebo tablet in the morning and evening for 7 days. This phase provided a washout period for other psychotropic drugs and allowed those who could not tolerate placebo or those who had a placebo response (patients whose total 17-item HAM-D scores were <20 or decreased more than 20% from screening to baseline) to be discontinued from the study.

Patients returned to the clinic after the 1-week placebo period for baseline assessments. Those who continued to meet study eligibility requirements were randomized to one of three treatment groups: bupropion SR 150 mg/d (150 mg QD), bupropion SR 300 mg/d (150 mg BID), or placebo. Patients assigned to bupropion SR 300 mg/d were given a dose-escalation regimen consisting of bupropion SR 150 mg QD on days 1 to 3 followed by bupropion SR 300 mg/d on days 4 to 56. All patients received the same number of identical-appearing tablets.

Efficacy Measures

At the baseline visit (day 0) and at each weekly visit during the treatment period, the following physician-rated assessments of depression were conducted: the 17-item HAM-D and the Clinical Global Impressions for Severity of Illness (CGI-S) and Clinical Global Impressions for Improvement of Illness (CGI-I)[18] scales. The 17-item HAM-D measures the severity of symptoms in patients with a diagnosis of depression. The CGI-S scale is a clinical assessment of overall severity of illness based on a seven-point scale ranging from 1 (normal) to 7 (among the most extremely ill patients). The CGI-I scale is an overall rating of improvement based on a seven-point scale ranging from 1 (very much improved) to 7 (very much worse).

Safety Measures

At each clinic visit, vital signs and weight were measured, and reports of adverse events (defined as any untoward medical occurrence, potentially drug related or not) were elicited through a standard verbal probe concerning any difficulties or unusual occurrences. Investigators were instructed to always ask the same question when conducting the verbal probe to ensure uniformity between patients,

study visits, and study sites. At the final visit (day 56 or discontinuation), physical examination and clinical laboratory tests were repeated. If an ECG had been performed at baseline, this was also repeated at the final visit.

Statistical Analyses

Mean rates of compliance were derived by calculating individual compliance rates (determined by counting returned tablets at each study visit) during the treatment period (expressed as a percentage) and taking the average for each treatment group. For the 17-item HAM-D and CGI-S scores, statistical analyses were performed on the mean change from baseline. Raw scores were used for the CGI-I analyses. Analyses were performed using analysis of variance (ANOVA) contrasts for all patients who received at least one dose of study medication and had at least one treatment-phase efficacy assessment. Patients who discontinued the study prematurely had last observations carried forward (LOCF) to each successive scheduled efficacy assessment. All data were reported using LOCF values because observed values can be influenced markedly by differential dropout rates between responding and nonresponding patients. Two-sided tests and/or confidence intervals with an $\alpha = 0.05$ were used for treatment comparisons.

The safety of bupropion SR versus placebo was analyzed for all patients who received at least one dose of study drug and had at least one treatment-phase safety assessment. This was done by coded tabulation of adverse events and by the assessment of clinically significant changes in pretreatment and posttreatment vital signs, weight, ECG findings, physical findings, and clinical laboratory values. Between-treatment-group differences in changes in vital signs from baseline to the end of the study (day 56) were tested for statistical significance by ANOVA.

RESULTS

Demographic and Baseline Characteristics

Three hundred sixty-two patients completed the single-masked placebo phase of the study and were randomized to treatment with bupropion SR 150 mg/d (BUP-150; n = 121), bupropion SR 300 mg/d (BUP-300; n = 120), or placebo (n = 121). Nine patients randomized to treatment had no data beyond baseline and were excluded from all efficacy and safety analyses, leaving a primary study population of 353 patients.

Baseline demographic characteristics and psychiatric histories of the primary study population are shown in Table I. All patients had a DSM III-R diagnosis of major depression, with the majority experiencing a recurrent episode of depression. For most patients, the duration of the current depressive episode had been 6 months or longer. Between 88% and 90% of patients in each treatment group were rated as moderately depressed; the remainder were classified as severely depressed.

The total compliance rate (total dose taken/total dose prescribed) was 97% for the BUP-150 group and 98% for both the BUP-300 and placebo groups. The mean daily doses were 147 and 290 mg for the BUP-150 and BUP-300 groups, respectively.

Of the 362 patients randomized to treatment, 168 (46%) were prematurely discontinued from the study: 55 (45%)

Table I. Baseline demographic characteristics and psychiatric histories of the primary study population.

Characteristic	BUP-150 (n = 120)	BUP-300 (n = 116)	Placebo (n = 117)
Sex, no. (%)			
Male	34 (28)	24 (21)	48 (41)
Female	86 (72)	92 (79)	69 (59)
Age (y)			
Mean ± SD	38.3 ± 11.0	38.6 ± 10.7	40.2 ± 12.2
Range	19–72	18–64	19–69
Race, no. (%)			
White	100 (83)	100 (86)	100 (85)
Black	6 (5)	3 (3)	9 (8)
Other	14 (12)	13 (11)	8 (7)
Diagnosis of current depressive episode, no. (%)			
Single	44 (37)	50 (43)	43 (37)
Recurrent	76 (63)	66 (57)	74 (63)
No. of previous depressive episodes, no. (%)			
1	29 (38)	33 (50)	24 (32)
2	12 (16)	8 (12)	22 (30)
3	6 (8)	3 (5)	7 (9)
4	4 (5)	2 (3)	3 (4)
>4	25 (33)	20 (30)	18 (24)
Rating of current depressive episode, no. (%)			
Moderate	105 (88)	102 (88)	105 (90)
Severe	15 (13)	14 (12)	12 (10)
Duration of current depressive episode, no. (%)			
1–2 mo	12 (10)	13 (11)	11 (9)
3–6 mo	43 (36)	30 (26)	24 (21)
7–12 mo	32 (27)	31 (27)	36 (31)
13–24 mo	33 (28)	42 (36)	46 (39)

BUP-150 = sustained-release bupropion 150 mg/d; BUP-300 = sustained-release bupropion 300 mg/d.

of the 121 BUP-150 patients, 53 (44%) of the 120 BUP-300 patients, and 60 (50%) of the 121 placebo patients. A higher proportion of patients receiving placebo (22%) than either BUP-150 (12%) or BUP-300 (10%) were discontinued because of an inadequate response to study medication or because their condition deteriorated; however, more patients in the BUP-150 (8%) and BUP-300 (11%) groups than in the placebo group (3%) were discontinued because of an adverse event (nonsignificant). The remainder of premature discontinuations were because patients withdrew consent, violated the study protocol, or were lost to follow-up, with similar proportions across treatment groups.

Efficacy Evaluation

17-Item HAM-D

Mean 17-item HAM-D scores at baseline were similar between groups. The bupropion SR groups had significantly greater improvement in 17-item HAM-D scores compared with placebo ($P \leq 0.05$) by the end of the study (day 56) (Figure 1).

CGI-S Scale

All three treatment groups had a mean CGI-S rating of 4.4 at baseline. The bupropion SR groups had significantly greater improvement in CGI-S scores compared with placebo ($P \leq 0.05$) by the end of the study (day 56) (Figure 2).

CGI-I Scale

The bupropion SR groups had significantly lower scores compared with placebo ($P \leq 0.01$) by the end of the study (day 56) (Figure 3).

Safety Evaluation

As determined by the study investigators, who remained masked to treatment until the study and all data analyses were complete, no clinically significant differences in mean systolic or diastolic blood pressure or heart rate were observed from baseline to day 56 between either of the bupropion SR groups and the placebo group. No clinically significant differ-

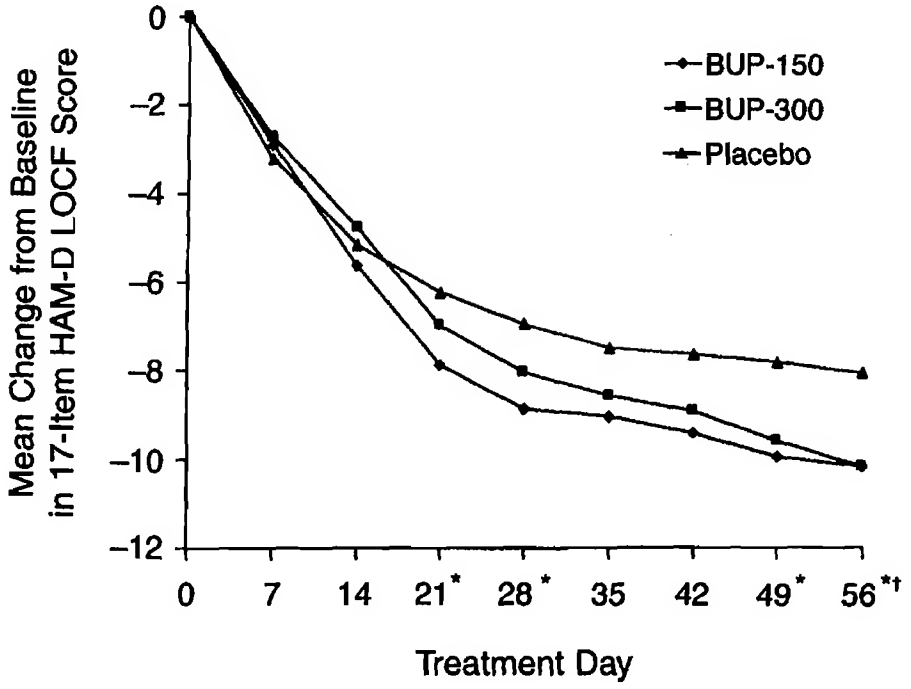


Figure 1. Mean change from baseline in scores on the 17-item Hamilton Rating Scale for Depression (HAM-D) by treatment day. Scores are last observations carried forward (LOCF). BUP-150 = sustained-release bupropion 150 mg/d (150 mg QD); BUP-300 = sustained-release bupropion 300 mg/d (150 mg BID). *$P \leq 0.05$ BUP-150 versus placebo; †$P \leq 0.05$ BUP-300 versus placebo.

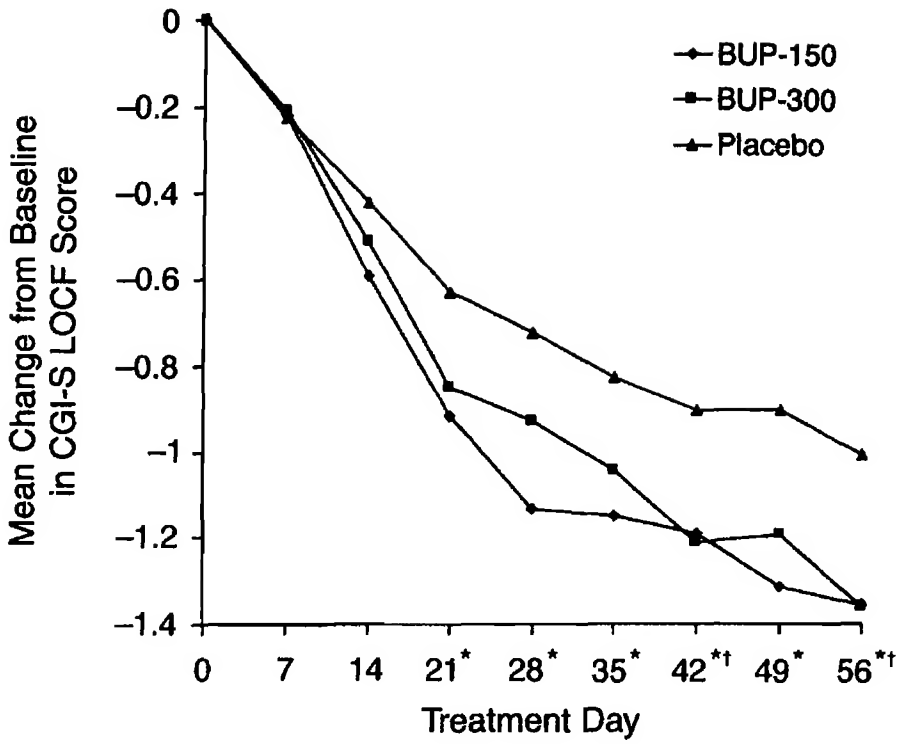


Figure 2. Mean change from baseline in scores on the Clinical Global Impressions for Severity of Illness (CGI-S) scale by treatment day. Scores are last observations carried forward (LOCF). BUP-150 = sustained-release bupropion 150 mg/d (150 mg QD); BUP-300 = sustained-release bupropion 300 mg/d (150 mg BID). $^{*}P \leq 0.05$ BUP-150 versus placebo; $^{\dagger}P \leq 0.05$ BUP-300 versus placebo.

ences in clinical laboratory evaluations, ECG findings, or physical findings were observed from baseline to day 56 between either bupropion SR group and the placebo group.

The most frequently reported adverse events (≥10% of patients in any group), regardless of perceived relationship to study drug, are shown in Table II. Headache was the most frequently reported adverse event in all treatment groups. More than twice as many patients in the BUP-300 group as in the BUP-150 group reported sweating and constipation as adverse events. Only one adverse event related to sexual dysfunction was reported: impotence in a male patient in the BUP-150 group. Across all treatment groups, the majority (95%) of adverse events were rated by investigators as being mild or moderate in intensity.

Only one serious adverse event was reported during the study. A patient who had been randomized to placebo was treated in the emergency department for an overdose of 18 placebo tablets and unknown quantities of an antibiotic and a nonsteroidal anti-inflammatory agent. The patient was hospitalized for further treatment of depression and was discontinued from the study.

Overall, 27 patients (10 [8%] BUP-150, 13 [11%] BUP-300, 4 [3%] placebo) were discontinued from the study prematurely

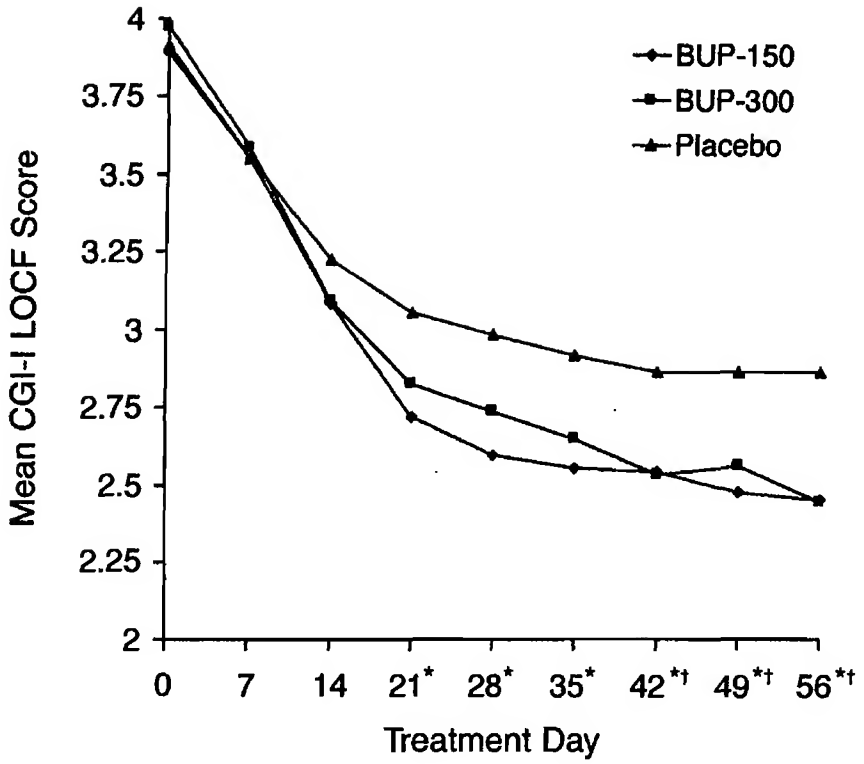


Figure 3. Mean scores on the Clinical Global Impressions for Improvement of Illness (CGI-I) scale by treatment day. Scores are last observations carried forward (LOCF). BUP-150 = sustained-release bupropion 150 mg/d (150 mg QD); BUP-300 = sustained-release bupropion 300 mg/d (150 mg BID). *$P \leq 0.05$ BUP-150 versus placebo; †$P \leq 0.05$ BUP-300 versus placebo.

Table II. Percentages of patients reporting adverse experiences.*

Adverse Experience	BUP-150 (n = 120)	BUP-300 (n = 116)	Placebo (n = 117)
Headache	21.7	24.1	18.0
Dry mouth	13.3	16.4	6.0
Sweating	4.2	11.2	1.7
Constipation	5.0	10.3	6.8
Nausea	9.2	10.3	6.0

BUP-150 = sustained-release bupropion 150 mg/d; BUP-300 = sustained-release bupropion 300 mg/d.
*Reported by ≥10% of patients in any treatment group.

because of an adverse event. The most common adverse events leading to discontinuation in the bupropion SR groups involved skin conditions (8 [3%], mainly rash), nervous system conditions (5 [2%], agitation and insomnia), and gastrointestinal conditions (4 [2%], nausea and constipation).

Weight loss was observed in both bupropion SR groups compared with placebo. Mean weight at baseline was similar across treatment groups and ranged from 76 to 79 kg. The largest decrease in mean weight between baseline and discontinuation (–1.0 kg) was seen in the BUP-300 group, followed by the BUP-150 group (–0.5 kg); the mean weight of the placebo group remained relatively unchanged (–0.2 kg). There was a statistically significant difference in mean weight change between the BUP-300 and placebo groups throughout the study ($P \leq 0.001$). A statistically significant difference between the BUP-150 and placebo groups was observed on assessment days 7 through 42 ($P \leq 0.05$). A total of 45 patients had a >2.3-kg weight change between baseline and discontinuation. Thirty-eight (11 BUP-150, 18 BUP-300, and 9 placebo) patients lost more than 2.3 kg, and 8 patients (2 BUP-150, 2 BUP-300, and 4 placebo) gained more than 2.3 kg.

DISCUSSION AND CONCLUSIONS

Results of this study demonstrate that the SR formulation of bupropion is effective and well tolerated in the treatment of moderate-to-severe depression. Both bupropion SR doses (150 and 300 mg/d) were more effective than placebo in improving the symptoms of depression, and once-daily dosing with bupropion SR 150 mg appeared to be at least as effective as twice-daily dosing. At the end of the treatment period, BUP-150 and BUP-300 patients had depression scores that were significantly lower than with placebo on all rating scales for depression (17-item HAM-D, CGI-S, and CGI-I). This study clearly demonstrates the efficacy of bupropion SR versus placebo. Extending these findings, Kavoussi et al[19] demonstrated comparable efficacy between bupropion SR and a commonly prescribed SSRI, sertraline.

In the present study, the lower, once-daily dose of bupropion SR (150 mg) provided relief from symptoms of depression at least as effectively as the higher, twice-daily dose (300 mg). This is an important consideration in the treatment of a disorder that for many patients is a chronic, recurrent condition requiring medication on a regular and long-term basis.[20] Both once- and twice-daily dosing regimens of bupropion SR offer improvements in patient convenience and compliance over the previous bupropion IR formulation, which is administered three times daily. The ability to administer an effective antidepressant medication on a once- or twice-daily dosing schedule is important, given that more frequent daily dosing has been associated with patient noncompliance,[21] resulting in an incomplete therapeutic response.[22,23]

Numerous studies have established the effectiveness and tolerability of bupropion IR for the treatment of depression and have documented its efficacy and safety compared with placebo and other antidepressants.[7,12,13,24–26] Bupropion IR has been shown to be as effective as amitriptyline, doxepin, fluoxetine, trazodone, nortriptyline, and imipramine,[5,6,8,27–30] without having the anticholinergic, antihistaminic, and cardiovascular side effects observed with these agents.[6,13,31,32] Bupropion IR has been shown to have an

adverse event profile similar to that of placebo[13,26,27,32] without causing sedation, cognitive impairment, or sexual dysfunction.[33–35]

In this study, bupropion SR had a favorable safety profile at both 150 mg/d and 300 mg/d. The most common adverse experiences were headache, dry mouth, sweating, constipation, and nausea. More than twice as many patients receiving bupropion SR 150 mg/d complained of sweating and constipation compared with those receiving bupropion SR 300 mg/d, suggesting that these events may be dose related. Although dry mouth occurred in more than twice as many patients treated with either dose of bupropion SR as with placebo, it was of mild-to-moderate severity and did not appear to be related to an anticholinergic effect of bupropion. Sexual dysfunction, a significant effect of treatment with SSRIs[19,36] that is probably related to their serotoninergic activity,[37] was reported in only one patient (BUP-150) in the current study. No serious adverse experiences were reported in either bupropion SR group, and no clinically significant changes from baseline were found in these patients' vital signs, laboratory variables, ECG findings, or physical findings.

Both bupropion SR groups had an overall mean weight loss; 1.0 kg for the BUP-300 group and 0.5 kg for the BUP-150 group. These findings are consistent with studies using bupropion IR, where mean weight losses of approximately 0.9 kg were typically reported for doses ≥300 mg/d.[5,7,24,28,32,38] The weight loss reported with bupropion use may be considered advantageous, since weight gain is often seen by patients as a negative effect that can result in compliance problems.[38,39] TCAs tend to produce average weight gains ranging from 1.4 to 2.7 kg after ≤13 weeks of treatment, and larger gains have been reported after longer treatment periods.[6,28,38]

In summary, this placebo-controlled study demonstrates that bupropion SR 150 mg/d (150 mg QD) or 300 mg/d (150 mg BID) is an effective and well-tolerated antidepressant therapy in patients with moderate-to-severe depression. Because bupropion SR 150 mg may be administered either once or twice daily with at least equal effectiveness, patients may benefit from the convenience and improved tolerability associated with once-daily dosing. Treatment with bupropion SR for 8 weeks was also associated with an overall mean weight loss.

ACKNOWLEDGMENT

This research was supported by a grant from Glaxo Wellcome Inc., Research Triangle Park, North Carolina.

Address correspondence to: Frederick W. Reimherr, MD, Department of Psychiatry, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132.

REFERENCES

1. Regier D, Boyd JH, Burke JD, et al. One-month prevalence of mental disorders in the United States: Based on five epidemiologic catchment area sites. *Arch Gen Psychiatry.* 1988;45:977–986.

2. Montano CB. Recognition and treatment of depression in a primary care setting. *J Clin Psychiatry.* 1994;55(Suppl):18–34.

3. Stokes PE. A primary care perspective on management of acute and long-term depression. *J Clin Psychiatry.* 1993;54(Suppl): 74–84.

4. Fabre LF, Brodie KH, Garver D, Zung WWK. A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. *J Clin Psychiatry.* 1983; 44:88–94.

5. Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psychiatry.* 1991;52:329–335.

6. Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol.* 1986;6:27–32.

7. Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry.* 1990;51:194–199.

8. Weisler RH, Johnston JA, Lineberry CG, et al. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol.* 1994;14: 170–179.

9. Ascher JA, Cole JO, Colin J, et al. Bupropion: A review of its mechanism of antidepressant activity. *J Clin Psychiatry.* 1995;56:395–401.

10. Ferris RM, Cooper BR. Mechanism of antidepressant activity of bupropion. *J Clin Psychiatry Monograph.* 1993;11:2–14.

11. Preskorn SH, Burke M. Somatic therapy for major depressive disorder: Selection of an antidepressant. *J Clin Psychiatry.* 1992;53(Suppl 9):5–18.

12. Van Wyck Fleet J, Manberg PJ, Miller LL, et al. Overview of clinically significant adverse reactions to bupropion. *J Clin Psychiatry.* 1983;44:191–196.

13. Zung WWK, Brodie HKH, Fabre L, et al. Comparative efficacy and safety of bupropion and placebo in the treatment of depression. *Psychopharmacology.* 1983;79: 343–347.

14. Bupropion (Wellbutrin SR®) product information. Glaxo Wellcome Inc., Research Triangle Park, North Carolina, 1996.

15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed., revised. Washington, DC: American Psychiatric Association; 1987:228–230.

16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56–62.

17. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1968;6:278–296.

18. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* DHEW Publication No. 76-338. Rockville, Md: National Institute of Mental Health, 1976:217–222.

19. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry.* 1997;58:532–537.

20. Keller MG, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: A 5-year prospective survey of 431 subjects. *Arch Gen Psychiatry.* 1992;49:809–816.

21. Greenberg RN. Overview of patient compliance with medication dosing: A literature review. *Clin Ther.* 1984;6:592–599.

22. Becker MH, Maiman LA. Strategies for enhancing patient compliance. *J Community Health.* 1980;6:113–135.

23. Cramer JA, Mattson RH, Prevey ML, et al. How often is medication taken as prescribed? A novel assessment technique. *JAMA.* 1989;261:3273–3277.

24. Feighner JP, Meredith CH, Stern WC, et al. A double-blind study of bupropion and placebo in depression. *Am J Psychiatry.* 1984;141:525–529.

25. Halaris AE, Stern WC, Van Wyck Fleet J, Reno RM. Evaluation of the safety and efficacy of bupropion in depression. *J Clin Psychiatry.* 1983;44:101–103.

26. Pitts WM, Fann WE, Halaris AE, et al. Bupropion in depression: A tri-center placebo-controlled study. *J Clin Psychiatry.* 1983;44:95–100.

27. Branconnier RJ, Cole JO, Ghazvinian S, et al. Clinical pharmacology of bupropion and imipramine in elderly depressives. *J Clin Psychiatry.* 1983;44:130–133.

28. Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. *J Clin Psychiatry.* 1983;44:121–129.

29. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44:118–120.

30. Othmer E, Othmer SC, Stern WC, Van Wyck Fleet J. Long-term efficacy and safety of bupropion. *J Clin Psychiatry.* 1983;44:153–156.

31. Wenger TL, Stern WC. The cardiovascular profile of bupropion. *J Clin Psychiatry.* 1983;44:176–182.

32. Zung WWK. Review of placebo-controlled trials with bupropion. *J Clin Psychiatry.* 1983;44:104–114.

33. Gardner EA, Johnston JA. Bupropion—an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol.* 1985:5:24–29.

34. Nemeroff CB. Evolutionary trends in the pharmacotherapeutic management of depression. *J Clin Psychiatry.* 1994;55(Suppl 12):3–15.

35. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *J Clin Psychiatry.* 1993;54: 459–465.

36. Segraves RT. Overview of sexual dysfunction complicating the treatment of depression. *J Clin Psychiatry Monograph.* 1992;10:4–10.

37. Meston CM, Gorzalka BB. Psychoactive drugs and human sexual behavior: The role of serotonergic activity. *J Psychoact Drugs.* 1992;24:1–40.

38. Harto-Truax N, Stern WC, Miller LL, et al. Effects of bupropion on body weight. *J Clin Psychiatry.* 1983;44:183–186.

39. Gardner EA. Management of the depressed patient: The art and science of compliance. Part IV: Patient compliance in antidepressant treatment. *J Clin Psychiatry Monograph.* 1982;5:19.

EXHIBIT D

Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care

Ulla M. Lepola[a,b], Henrik Loft[c] and Elin Heldbo Reines[c]

Escitalopram was compared to placebo in moderately to severely depressed patients in primary care with citalopram as the active reference. Patients were randomized to receive flexible doses of 10–20 mg/day escitalopram ($n=155$), 20–40 mg/day citalopram ($n=160$), or placebo ($n=154$) over an 8-week double-blind period. The primary efficacy parameter was the change from baseline to last assessment in the Montgomery–Asberg Depression Rating Scale total score. Escitalopram produced a statistically significant therapeutic difference of 2.9 points ($P=0.002$) compared to placebo, and escitalopram was consistently and statistically significantly more efficacious than placebo from week 1 onwards. Analysis of Clinical Global Impression–Severity and Clinical Global Impression–Improvement confirmed the primary efficacy results. By week 8, significantly more patients had responded to treatment with escitalopram than with citalopram ($P=0.021$) or placebo ($P=0.009$). Escitalopram was as well tolerated as citalopram and had a similar adverse event profile. Both escitalopram- and citalopram-treated patients had placebo-level adverse event withdrawal rates (3% and 4%, respectively). This study demonstrates the consistent antidepressant efficacy and excellent tolerability of escitalopram 10–20 mg/day in primary care patients with major depressive disorder. *Int Clin Psychopharmacol* 18:211–217 © 2003 Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2003, 18:211–217

Keywords: antidepressant, citalopram, efficacy, enantiomer, escitalopram, flexible dose, MADRS, major depressive disorder, SSRI

[a]Kuopion Psykiatripalvelu OY Psychiatric Research, Clinic of Kuopio, Kuopio, Finland, [b]Department of Psychiatry, Oulu and Helsinki University, Finland and [c]H. Lundbeck A/S, International Clinical Research, Copenhagen Valby, Denmark.

Correspondence and requests for reprints to Henrik Loft, H. Lundbeck A/S, International Clinical Research, 9 Ottiliavej, DK-2500 Copenhagen Valby, Denmark.
Tel: +45 36 43 23 04; fax: +45 36 43 82 96;
e-mail: hlo@lundbeck.com

Received 4 February 2003 Accepted 8 April 2003

Introduction

Depression is a serious illness associated with considerable morbidity, risk of suicide and adverse social consequences (Coryell *et al.*, 1993; Montgomery *et al.*, 1994; Bostwick and Pankratz, 2000), and it is the major cause of years lost to disability (Murray and Lopez, 1997). An estimated 6 to 17% of primary care patients suffer from major depression (Katon *et al.*, 1992); however, only approximately 50% of these patients seek medical assistance and less than 10% receive the appropriate treatment (Lepine *et al.*, 1997). The lifetime risk of a woman developing major depressive disorder (MDD) varies from 10% to 25% and, for a man, the risk varies from 5% to 12% (DSM-IV) (American Psychiatric Association, 1994).

Escitalopram is the *S*-enantiomer of citalopram and is the most selective serotonin reuptake inhibitor (SSRI) (Owens *et al.*, 2001). The antidepressant activity of escitalopram was observed in animal models of depression (Hyttel *et al.*, 1992; Mørk *et al.*, 2002) with evidence of a higher potency than that of citalopram (Sánchez *et al.*, 2003).

Clinical studies showed that escitalopram 10 mg/day is an effective and well tolerated treatment for MDD in primary care (Wade *et al.*, 2002) and in specialist settings (Burke *et al.*, 2002). Analysis of the data from the first 4 weeks of this study (during the fixed dose period of 10 mg/day escitalopram and 20 mg/day citalopram) showed evidence of an early effect by escitalopram (Montgomery *et al.*, 2001).

We present data from the entire 8-week study, in which the efficacy and tolerability of flexible doses of 10–20 mg/day escitalopram were compared to placebo in patients with MDD in primary care. Citalopram was selected as the active reference because escitalopram is the therapeutically active enantiomer of citalopram, for which safety and efficacy are well established.

Methods

This study was conducted in primary care centres in Belgium, Canada, Finland, France, Norway, Sweden, Switzerland and the UK. It was carried out in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki (1997), and according to the local regulations in each participating country. Local ethics committees approved the study and eligible patients provided their written informed consent before participating.

0268-1315 © 2003 Lippincott Williams & Wilkins

DOI: 10.1097/01.yic.0000074988.54339.7c

Study design

This was a double-blind, randomized, parallel-group, flexible-dose, 8-week study comparing escitalopram with placebo in patients with MDD (diagnosed according to DSM-IV criteria) in primary care, using citalopram as the active reference. There was an initial 1-week single-blind placebo period, followed by randomization of eligible patients in a 1 : 1 : 1 ratio of escitalopram, citalopram and placebo treatment. During the first 4 weeks of the double-blind treatment period, patients took either 10 mg escitalopram, 20 mg citalopram or placebo as one tablet daily. If a patient's response was unsatisfactory, or if there was an aggravation of the depression, based on the Clinical Global Impression–Severity (CGI–S) score, investigators had the option of doubling the dosage at week 4 or week 6.

Patients

Patients of either sex were eligible for the study if they fulfilled the DSM-IV criteria for MDD, had a baseline Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score ≥ 22 and ≤ 40, and were aged between 18 and 65 years. Investigators also screened patients on the basis of physical examination, medical history, electrocardiogram (ECG) and clinical laboratory tests.

Patients were ineligible for the study if they met any of the following criteria: suffering from mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive–compulsive disorder, eating disorders, mental retardation, any pervasive developmental disorder or cognitive disorder (according to DSM-IV criteria), MADRS score ≥ 5 on item 10 (suicidal thoughts), treatment with antipsychotics, antidepressants, hypnotics, anxiolytics (except benzodiazepines for insomnia), barbiturates, chloral hydrate, or other 5-hydroxytryptamine receptor agonists, electroconvulsive treatment, treatment with behaviour therapy or psychotherapy.

Evaluations

Patients were evaluated using the following rating scales: MADRS, CGI–S and Clinical Global Impression–Improvement (CGI–I) (Guy, 1976), recorded at screening, at baseline (end of single-blind placebo treatment, except CGI-I), and 1, 2, 3, 4, 6 and 8 weeks after starting double-blind treatment. Efficacy parameters included the proportion of responders (patients with $\geq 50\%$ decrease in MADRS total score from baseline to last assessment).

Safety was evaluated on the basis of adverse events, clinical laboratory tests, ECG and physical examination (including vital signs and weight).

Statistical analysis

The sample size for the primary analysis was based on the expected change from baseline to last assessment in the MADRS total score between escitalopram and placebo. Assuming a standardized effect size (MIREDIF/SD = minimum relevant difference divided by SD) of 0.40, 155 patients per group were expected to provide a power of at least 90% at the 5% level.

Efficacy analyses were conducted for the full-analysis set (FAS) (also known as the intent-to-treat population), which included all randomized patients who took at least one dose of double-blind study medication, and who had at least one valid post-baseline assessment of their MADRS total score.

The primary efficacy analysis was performed using the principle of last observation carried forward (LOCF). The statistical method was analysis of covariance (ANCOVA) with factors for treatment group and centre, and baseline MADRS total score as a covariate.

The change from baseline in MADRS total score, and CGI–S score, and the CGI–I score were analysed for each visit using a model similar to the primary analysis model. Statistical test results are presented per visit, based on observed cases (OC), and also based on LOCF for week 8. Other ad-hoc analyses were performed using ANCOVA and logistic regression.

Statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

Results

Patient population

Of the 471 patients who were randomized into double-blind treatment, 468 took at least one dose of double-blind study medication, had at least one valid post-baseline assessment of the MADRS total score and comprised the FAS ($n = 154$ for placebo; $n = 159$ for citalopram; $n = 155$ for escitalopram).

Baseline characteristics

The patient demographics and baseline characteristics are shown in Table 1. There were no clinically relevant differences between treatment groups. The severity of depression was distributed similarly between the treatment groups at baseline: approximately 58% of the patients were moderately ill (MADRS ≥ 22 and ≤ 29) and approximately 42% of the patients were severely ill (MADRS ≥ 30).

Withdrawals

The overall withdrawal rate (approximately 7%) was very low and similar for each treatment group (percentage of patients who completed the study: 90% in the placebo group, 94% in the escitalopram group, and 95% in the citalopram group) (Table 2). The two most frequently reported reasons for withdrawal were adverse events and

Table 1 Patient demographics and baseline characteristics

	Placebo (n=154)	Escitalopram (n=155)	Citalopram (n=160)
Sex			
Women (%)	111 (72.1)	116 (74.8)	111 (69.4)
Age (years)			
Mean ± SD	43 ± 12	43 ± 11	44 ± 11
Body mass index (kg/m^2)			
Mean ± SD	26.9 ± 6.2	25.6 ± 5.6	26.4 ± 4.9
Baseline severity of depression			
Mean MADRS	28.7	29.0	29.2
Mean CGI-S	4.22	4.34	4.30

MADRS, Montgomery–Asberg Depression Rating Scale; CGI-I, Clinical Global Impression–Improvement.

Table 2 Patients withdrawn from the study

	Placebo (n=154)	Escitalopram (n=155)	Citalopram (n=160)
Withdrawal for all reasons (%)	15 (9.7)	9 (5.8)	8 (5.0)
Due to adverse events (%)	4 (2.6)	4 (2.6)	6 (3.8)
Due to lack of efficacy (%)	5 (3.2)	0 (0)	1 (0.6)
Other (%)	6 (3.9)	5 (3.2)	1 (0.6)

lack of efficacy. No escitalopram-treated patients withdrew due to lack of efficacy.

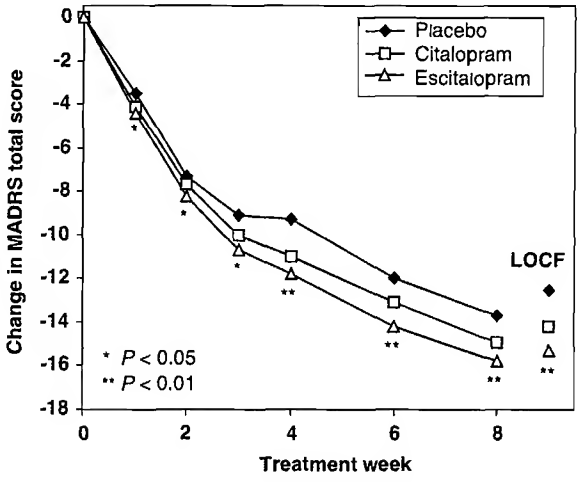
MADRS, CGI-S and CGI-I scores

The primary efficacy analysis demonstrated a mean change in MADRS total score from baseline to last assessment (LOCF) of 15.0. points in the escitalopram group, 13.6 points in the citalopram group and 12.1 points in the placebo group (Fig. 1). The 2.9-point (SE 0.93) difference in favour of escitalopram, compared to placebo, was statistically significant ($P = 0.002$). All MADRS single items for escitalopram showed improvement compared to placebo at last assessment (LOCF), and six of the 10 items were statistically significant (Fig. 2).

Therapeutic superiority of escitalopram over placebo was not only shown by the MADRS total score from week 1 onwards, but also by the two CGI scales: severity and improvement (CGI-S and CGI-I). Escitalopram was statistically significantly better than placebo on the CGI-S score as early as week 1 (Fig. 3), and analysis of CGI-I for escitalopram showed statistically significant improvements relative to placebo at post-baseline assessments from week 1 onwards (Fig. 4). Thus, statistically significant separation from placebo was seen on all three scales from week 1 (Figs 1, 3 and 4). Escitalopram was numerically better than citalopram at all time points on all three efficacy scales.

Citalopram was numerically, but not statistically significantly better than placebo from week 1, based on the mean change in MADRS total score from baseline (Fig. 1). Numerical superiority of citalopram over placebo was found for all 10 items; statistical superiority ($P < 0.05$) was only found for item 3 (inner tension) (Fig. 2). Citalopram was statistically significantly better than placebo on the CGI-I scale at week 8 (OC) and at last assessment (LOCF) (Fig. 4).

Fig. 1

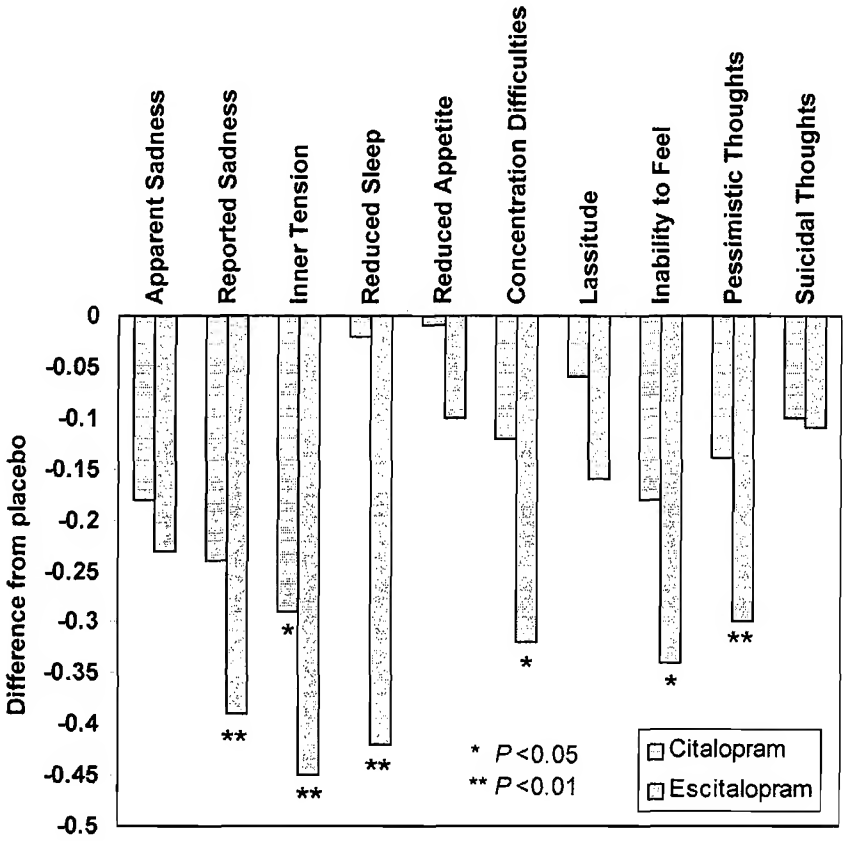


Adjusted mean changes from baseline in Montgomery–Asberg Depression Rating Scale (MADRS) total scores by week (observed cases, OC).

Responders and remitters

Responders were patients with ≥ 50% decrease in MADRS total score from baseline to last assessment. Significantly more escitalopram-treated patients responded (63.7%) by week 8 (FAS, OC) than either placebo-treated (48.2%; $P = 0.009$, logistic regression) or citalopram-treated patients (52.6%; $P = 0.021$, logistic regression). Analysis of time to response revealed that, based on median survival times, escitalopram-treated patients were responders some 8.1 days faster than

Fig. 2



Difference from placebo from baseline to week 8 (last observation carried forward, LOCF) for Montgomery–Asberg Depression Rating Scale (MADRS) single items. *Statistically significant difference between treatment and placebo groups ($P<0.05$, ANCOVA) **Statistically significant difference between treatment and placebo groups ($P<0.01$, ANCOVA).

citalopram-treated patients ($P < 0.05$). At endpoint, significantly more patients ($P < 0.036$: FAS, OC) treated with escitalopram (52.1%) than those treated with citalopram (42.8%) were in remission (MADRS < 12). In this analysis neither treatment separated significantly from placebo, but there was a trend for escitalopram ($P = 0.055$).

Dose

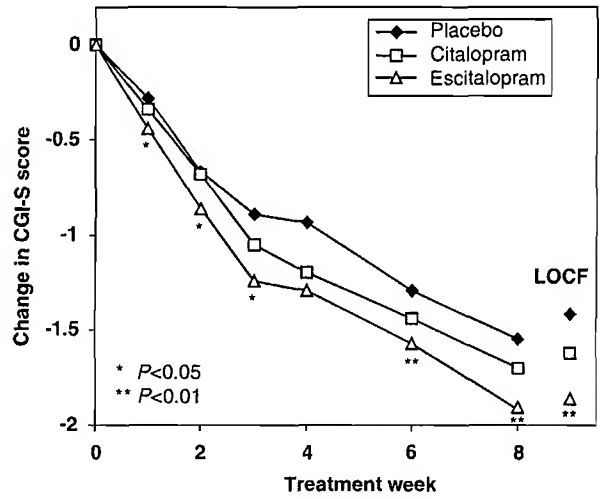
A dose increase was first allowed after the initial 4-week, fixed-dose period. The proportion of patients who had their doses increased was 50% in the placebo group, 43% in the citalopram group and 41% in the escitalopram group; the mean daily dose at week 8 was 14.0 mg in the escitalopram group and 28.4 mg in the citalopram group.

Tolerability

A low withdrawal rate (Table 2) and a low incidence of adverse events (Table 3) were reported for all three groups. The investigators considered the majority of adverse events to be mild or moderate and unrelated to treatment. Adverse events with an incidence greater than 5% in any treatment group and above placebo level are shown in Table 3. Nausea was the most frequent adverse event reported by escitalopram-treated patients and was mostly mild and transient. All other adverse events reported for escitalopram had an incidence of less than 10% of patients. Although more patients in the escitalopram group had insomnia and increased sweating than patients in the placebo group, none withdrew from the study for these reasons. All other adverse events with an incidence greater than 5% in the escitalopram group were at placebo levels. Of the 39 men randomized to escitalopram, two (5%) reported impotence as an adverse event (Table 3).

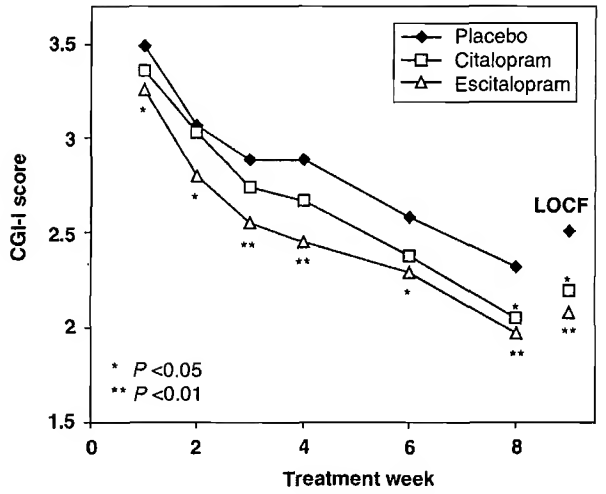
Analysis of mean weight change from baseline to last assessment for all patients showed that placebo-treated patients gained approximately 0.5 kg, which change was significantly greater than the very small increase in weight seen in either escitalopram-treated (0.03 kg,

Fig. 3



Adjusted mean changes from baseline in Clinical Global Impression–Severity (CGI-S) scores by week (observed cases, OC).

Fig. 4



Adjusted mean Clinical Global Impression–Improvement (CGI-I) scores by week (observed cases, OC).

$P < 0.040$) or citalopram-treated (0.04 kg, $P < 0.032$) patients.

There were no clinically relevant changes from baseline to last assessment in mean laboratory test values, vital signs or ECG, and there were no clinically relevant differences between treatment groups.

Discussion

The results from this study are in accordance with other similar studies, one performed in a specialist setting (Burke *et al.*, 2002) and one in primary care (Wade *et al.*, 2002), and confirm the efficacy of escitalopram in the treatment of patients suffering from depression (MDD, DSM-IV, 1994). The efficacy of citalopram versus placebo was demonstrated by the CGI–I results, showing that the study recruited appropriate, treatment-sensitive patients. Escitalopram at 10–20 mg/day was statistically significantly more efficacious than placebo, based on the primary efficacy endpoint (improvement in MADRS total score). Significant efficacy on the primary outcome variable is clinically relevant judged by the positive results on both clinical global scales and the responder analysis. The superiority of escitalopram was also supported by the observation that more placebo-treated patients than escitalopram-treated patients had their dose increased.

The statistically significant superiority of escitalopram in the responder analysis was not only versus placebo, but also versus citalopram, which is known to be an effective antidepressant (Feighner and Overø, 1999). This is a more important finding than superiority in a pooled analysis because the study was not designed to detect a difference between the two active compounds. There are few published placebo-controlled trials that also include a comparison of two antidepressants (Entsuah *et al.*, 2002), and it is rare to find a direct advantage for one active antidepressant compared with another in a placebo-controlled trial (Rudolph and Feiger, 1999).

Support for the superiority of escitalopram to citalopram comes from a pooled analysis of three 8-week, randomized, placebo-controlled studies (Gorman *et al.*, 2002). In the pooled analysis, escitalopram showed a significant improvement in depressive symptoms, compared to placebo, from as early as week 1 on all three scales. Citalopram, venlafaxine and mirtazapine have shown statistically significant differences from placebo in at least some measures of efficacy within the first 2 weeks of treatment (Stahl *et al.*, 2001). This early symptom improvement is important in the treatment of MDD because depression is associated with substantial suffering. It is generally accepted that early onset of symptom improvement increases patient adherence to treatment and reduces progression to chronic major depression (Stahl *et al.*, 2001).

The early effect of escitalopram is also seen in animal models of depression. In the chronic mild stress model of depression in rats (Montgomery *et al.*, 2001), escitalopram showed a significant separation from placebo earlier than that seen with citalopram. The biological rationale for the effect is linked to the observation that escitalopram

Table 3 **Adverse events with an incidence > 5% in any treatment group and greater than placebo**

	Placebo (n=154)	Escitalopram (n=155)	Citalopram (n=160)
Patients with adverse events (%)	92 (59.7)	108 (69.7)	104 (65.0)
Nausea (%)	14 (9.1)	27 (17.4)	23 (14.4)
Increased sweating (%)	3 (1.9)	12 (7.7)	9 (5.6)
Diarrhoea (%)	5 (3.2)	10 (6.5)	12 (7.5)
Insomnia (%)	3 (1.9)	10 (6.5)	7 (4.4)
Somnolence (%)	2 (1.3)	8 (5.2)	5 (3.1)
Impotence (% of male patients)	0 (0.0)	2 (5.1)	0 (0.0)
Dry mouth (%)	2 (1.3)	7 (4.5)	12 (7.5)
Rhinitis (%)	9 (5.8)	7 (4.5)	11 (6.9)

produces higher serotonin levels in the brain than citalopram (Mørk *et al.*, 2002). Nonclinical results show that the presence of the *R*-enantiomer in citalopram has an inhibitory effect on the activity of the *S*-enantiomer (escitalopram). Thus, the early symptom improvement seen in the clinical setting with escitalopram is consistent with the nonclinical results. Based on the mean change from baseline in MADRS total score and CGI scores, escitalopram also demonstrated numerically greater improvement in depressive symptoms compared to citalopram.

This study showed that escitalopram was significantly better than placebo on six of the 10 MADRS single items and was numerically better than placebo on all 10 single items. Because MADRS comprises the core symptoms found in all forms of depression, the single item results indicate that escitalopram is capable of treating a wide range of depressed patients.

Escitalopram is as well tolerated as citalopram, with a similarly favourable adverse event profile and placebo-level adverse event withdrawal rates. The safety of escitalopram was also confirmed by the results from vital signs, laboratory values and ECGs, which showed no clinically relevant mean changes during the trial.

This study confirms that escitalopram is an appropriate first-line treatment for depressed patients seen in primary care, with a tolerability profile as favourable as that of citalopram and a withdrawal rate due to adverse events at placebo level. Escitalopram shows statistically significant superiority to citalopram with respect to response (63.7% and 52.6%, respectively) and remission (52.1% and 42.8%, respectively). Escitalopram produced significant improvement in the mean change from baseline in the MADRS total score compared to placebo from week 1 onwards. This early symptom improvement offers real treatment advantages to depressed patients.

Acknowledgements

The authors gratefully acknowledge the contribution of the investigators in each of the 69 primary care centres in the study. We also wish to acknowledge Ross S. Baird for his assistance in preparing this manuscript. This study was sponsored by H. Lundbeck A/S.

References

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. (DSM-IV). Washington DC: American Psychiatric Association.

Bostwick JM, Pankratz VS (2000). Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* **157**:1925–1932.

Burke WJ, Gergel I, Bose A (2002). Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* **63**: 331–336.

Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL (1993). The enduring psychosocial consequences of mania and depression. *Am J Psychiatry* **150**:720–727.

Declaration of Helsinki (1997). Recommendations guiding medical physicians in biomedical research involving human subjects. *JAMA* **277**:925–926.

Entsuah R, Shaffer M, Zhang J (2002). A critical examination of the sensitivity of unidimensional subscales derived from the Hamilton Depression Rating Scale to antidepressant drug effects. *J Psychiatr Res* **36**:437.

Feighner JP, Overø K (1999). Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. *J. Clin. Psychiatry* **60**: 824–830.

Gorman JM, Korotzer A, Su G (2002). Efficacy comparison of escitalopram and citalopram in treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectrums* **7 (suppl 1)**:40–44.

Guy W (1976). *ECDU Assessment Manual for Psychopharmacology*, rev. edn. US Department of Health, Education and Welfare. Publication No. (ADM) 218-222. Rockville, MD: National Institutes of Mental Health.

Hyttel J, Bøgesø KP, Perregaard J, Sánchez C (1992). The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. *J Neural Transm* **88**:157–160.

Katon W, Schulberg H (1992). Epidemiology of depression in primary care. *Gen Hospital Psychiatry* **14**:237–248.

Lepine JP, Gastpar M, Mendlewicz J, Tylee A (1997). Depression in the community: the first pan-European study DEPRESS (Depression Research in European Society). *Int Clin Psychopharmacol* **12**:19–29.

Montgomery SA, Åsberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**:382–389.

Montgomery SA, Roberts A, Patel AG (1994). Placebo-controlled efficacy of antidepressants in continuation treatment. *Int Clin Psychopharmacol* **9 (suppl 1)**:49–53.

Montgomery SA, Loft H, Sánchez C, Reines EH, Papp M (2001). Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. *Pharmacol Toxicol* **88**:282–286.

Murray CJL, Lopez AD (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* **349**: 1498–1503.

Mørk A, Kreilgaard M, Sánchez C, Brennum LT, Wiborg O (2002). Escitalopram: a comparative study of the *in vitro* and *in vivo* 5-HT uptake inhibitory activity. *Int J Neuropsychopharm* **5(suppl 1)**:66.

Owens MJ, Knight DL, Nemeroff CB (2001). Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and *R*-fluoxetine. *Biol Psychiatry* **50**:345–350.

Rudolph RL, Feiger AD (1999). A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* **56**:171–181.

Sánchez C, Bergqvist PBF, Brennum LT, Gupta S, Hogg S, Larsen A, Wiborg O (2003). Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. *Psychopharmacology* **167**:353–362.

Stahl SM, Nierenberg AA, Gorman JM (2001). Evidence of early onset of antidepressant effect in randomised controlled trials. *J. Clin Psychiatry* **62 (suppl 4)**:17–23.

Wade A, Lemming OM, Hedegaard KB (2002). Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* **17**:95–102.